Experimental Evaluation of Antitumor Drugs in the USA and USSR and Clinical Correlations

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Experimental Evaluation of Antitumor Drugs

in the

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Editors:

United States:

Abraham Goldin
Ira Kline

Soviet Union:

Zoya P. Sof'ina
Anatoli B. Syrkin

List of collaborators who contributed material for this Monograph: [1]

G. Attassi, Institut Jules Bordet, 1, rue Héger Bordet, 1000 Brussels, Belgium

A. Barker, Battelle Memorial Institute, Columbus Laboratories, Columbus, Ohio

V. S. Bazhanov, All-Union Research Institute for the Search for New Antibiotics, Academy of Medical Sciences, Moscow, USSR

A. K. Belousova, Oncological Scientific Center, Academy of Medical Sciences, Moscow, USSR

A. E. Bogden, Department of Immunobiology, Mason Research Institute, Worcester, Massachusetts

V. A. Chernov, All-Union Research Chemical Pharmaceutical Institute, Moscow, USSR

J. Davenport, Charles Pfizer and Company, Inc., New York, New York

S. R. K. de Dennis, Wisconsin Alumni Fund, Madison, Wisconsin

Y. V. Dobrynin, Oncological Scientific Center, Academy of Medical Sciences, Moscow, USSR

L. E. Dudek, Hazelton Laboratories America, Inc., Vienna, Virginia

N. M. Emanuel, Institute for Chemical Physics, Academy of Sciences, Moscow, USSR

V. A. Filov, N. N. Petrov Institute for Oncology, Ministry of Public Health, Leningrad, USSR

J. Gargus, Hazelton Laboratories America, Inc. Vienna, Virginia

G. F. Gauze, All-Union Research Institute for the Search for New Antibiotics, Academy of Medical Sciences, Moscow, USSR

B. T. Garibjanian, A. L. Minjoyan Institute of Fine Organic Synthesis of Academy of Sciences of Armenian S.S.R., Yerevan, USSR

R. Geran, Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland

T. G. Glazkova, Oncological Scientific Center, Academy of Medical Sciences, Moscow, USSR

A. Goldin, Division of of Cancer Treatment, National Cancer Institute, Bethesda, Maryland

V. A. Gorbunova, Oncological Scientific Center, Academy of Medical Sciences, Moscow, USSR

J. H. M. Henderson, George Washington Carver Foundation, Tuskegee Institute, Tuskegee, Alabama

R. K. Johnson, Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland

I. Kline, Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland

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N. P. Konovalova, Institute for Chemical Physics, Academy of Sciences, Moscow, USSR

N. D. Lagova, Oncological Scientific Center, Academy of Medical Sciences, Moscow USSR

I. S. Levi, Oncological Scientific Center, Academy of Medical Sciences, Moscow, USSR

W. Lichter, University of Miami School of Medicine, Miami, Florida

V. A. Lyashenko All-Union Research Institute for the Search for New Antibiotics. Academy of Medical Sciences, Moscow, USSR

F. L. Minzenberger, Illinois Technological Research Institute, Chicago, Illinois

L. L. Malyugina, N. N. Petrov Institute for Oncology, Ministry of Public Health, Leningrad, USSR

I. Miller, Arthur D. Little Company, Inc., Cambridge, Massachusetts

S. M. Navashin, All-Union Research Institute for Antibiotics, Academy of Medical Sciences, Moscow, USSR

L. A. Ostrovskaya, Institute for Chemical Physics, Academy of Sciences, Moscow, USSR

V. Peake, Southern Research Institute, Birmingham, Alabama

N. I. Perevodchikova, Oncological Scientific Center, Academy of Medical Sciences, Moscow, USSR

A. M. Petrovsky, Institute of Control Problems, Academy of Sciences, Moscow, USSR

G. N. Platonova, Oncological Scientific Center, Academy of Medical Sciences, Moscow, USSR

Y. C. Pukhalskaya, Oncological Scientific Center, Academy of Medical Sciences, Moscow, USSR

F. M. Schabel, Jr., Southern Research Institute, Birmingham, Alabama

J. Schuller, Stanford Research Institute, Stanford University Medical Center, Stanford, California

A. Shefner, Illinois Technological Research Institute, Chicago, Illinois

M. Sherman, Battelle Memorial Institute, Columbus Laboratories, Columbus, Ohio

Y. N. Shkodinskaya, Oncological Scientific Center, Academy of Medical Sciences, Moscow, USSR

M. M. Sigel, University of Miami School of Medicine, Miami, Florida

Z. P. Sof'ina, Oncological Scientific Center, Academy of Medical Sciences, Moscow, USSR

N. Y. Sologub, Ukrainian Research Institute for Pharmacology and Toxicology, Kiev, USSR

A. B. Syrkin, Oncological Scientific Center, Academy of Medical Sciences, Moscow, USSR

P. Thayer, Arthur D. Little Company, Inc., Cambridge, Massachusetts

V. N. Vapnik, Institute of Control Problems, Academy of Sciences, Moscow, USSR

J. M. Venditti, Drug Evaluation Branch, Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland

I. Wodinsky, Arthur D. Little Company, Inc., Cambridge, Massachusetts

R. J. Woodman, Microbiological Associates, Bethesda, Maryland

N. P. Yavorskaya, Oncological Scientific Center, Academy of Medical Sciences, Moscow, USSR

L. A. Zaytseva, Oncological Scientific Center, Academy of Medical Sciences, Moscow, USSR

A. A. Zidermane, Institute for Organic Synthesis, Academy of Sciences of Latvian S.S.R., Riga, USSR

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FOREWORD

The "Agreement Between the USA and the USSR for Cooperation in Medical Science and Public Health," which was signed on 23 May 1972, by former Secretary of State, William P. Rogers, and the Soviet Minister of Health, Boris V. Petrovsky, provided the opportunity for collaborative research in cancer chemotherapy on an international basis. In the first USA–USSR Monograph "Methods of Development of New Antitumor Drugs," various aspects of the joint collaborative effort in anticancer drug development were described.

Cancer investigators of the United States and the Soviet Union have been actively engaged in a bilateral research program relating preclinical findings to clinical efficacy and have amassed a large body of data on exchanged drugs in a battery of experimental tumor test systems. The results of this effort have set a stage for the correlation of these test systems for anticancer drug screening. Thus as a natural sequence to the first Monograph, this publication presents another bank of information evolving from these joint studies. The experimental data are compared with respect to the use of common and different animal tumor test systems in both countries and are analyzed in relation to clinical activity to establish the possibility for prospective prediction of new drugs for clinical utility.

The positive results of programs summarized in this Monograph provide a tangible and important product of the American–Soviet cooperative effort in cancer research. Also of considerable significance is the exchange of scientists between the two nations that provides a means for the sharing of different methodologies being used and under development in both countries for the screening and subsequent preclinical testing of potentially useful anticancer agents.

Concrete accomplishments such as this Monograph pave the way for future success in joint American and Soviet oncologic studies.

Arthur C. Upton
Former Director, National Cancer Institute
National Institutes of Health
Public Health Service
U.S. Department of Health and
Human Services
Bethesda, Maryland 20205

Nikolai N. Blokhin
Academician, USSR Academy of
Medical Sciences
General Director, Oncological
Scientific Center
Academy of Medical Sciences,
Moscow, USSR

PREFACE

In the five years since the signing of the USA–USSR Agreement for Health Cooperation, successful implementation of the joint cancer program has been achieved through: 1) an exchange of scientists; 2) the exchange of data and information; 3) an exchange of antitumor drugs and biologic and technicologic materials; 4) joint research programs; and 5) joint publications.

In the program of the Division of Cancer Treatment, National Cancer Institute, a new screening program has recently been instituted that removes screening from the realm of random empiricism and replaces the process with an experimental approach. It involves a prescreen comprised of leukemia P388 and a "by-pass" of the prescreen for compounds indicated by surveillance of the world's literature to have high biologic interest. Compounds active against P388 or selected to by-pass it are introduced into a screening panel comprised of human colon, breast, and lung tumors growing as xenografts in athymic mice and corresponding murine tumors growing in conventional mice. The program is designed to determine definitively whether the new screening panel has the capacity to improve prediction for activity of drugs in humans with cancer, both with respect to tumors in general and for tumors of organ-specific sites.

In the Oncological Scientific Center of the USSR, Academy of Medical Sciences, among the transplantable tumors being used to select the new drugs, besides leukemia La and carcinoma 755, leukemia L1210 and Lewis lung tumor have been included in recent years. The in-depth study of active antitumor agents is being conducted on various highly differentiated, solid transplantable tumors of animals. For this purpose, tumors of the mammary gland, large intestine, lung, uterine cervix, and forestomach are being used. The most promising drugs are being studied on induced and spontaneous tumors in laboratory and domestic animals, as well as on human tumors growing in tissue culture. Great attention is being devoted to the study of the metabolism of the tumors and the mechanisms of action of the drugs. All these measures are directed at prediction of the effect of new antitumor agents in man.

The present Monograph encompasses the testing of 30 American and 28 Soviet drugs in a spectrum comprised of a diversity of experimental tumor types, with comprehensive biologic and mathematical analyses pertaining to possible prognoses for therapeutic effects against specific categories of human tumors. It is significantly contributory to the development of new approaches in the screening programs for antitumor drugs at the National Cancer Institute and the Oncological Scientific Center of the USSR Academy of Medical Sciences and to the collaborative effort in the conquest of cancer.

In conjunction with the editors, we wish to express our gratitude to the many investigators and laboratories who contributed to this collaborative program.

Vincent T. DeVita, Jr.
Director, National Cancer Institute
Director, Division of Cancer Treatment
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20205

Natalia I. Perevodchikova
Professor, Chief of Department of Chemotherapy
Oncological Scientific Center
Academy of Medical Sciences
Moscow, USSR

Introduction[1]

Systematic screening programs designed to find new chemotherapeutic agents that may be effective in the treatment of cancer were instituted in the United States and in the Soviet Union in the 1940's. In the United States, such programs were initiated at the National Cancer Institute in Bethesda, Maryland; Children's Cancer Research Foundation in Boston; Sloan-Kettering Institute for Cancer Research in New York City; Columbia University College of Physicians and Surgeons in New York City; Army Chemical Center at Edgewood, Maryland; Burroughs Wellcome Company in Tuckahoe, New York; and the Lederle Laboratories in Pearl River, New York (*1*).

In the USSR, systematic experimental programs for study of anticancer activity were begun at the N. N. Petrov Institute of Oncology in Leningrad and the Ordzhonikidze All-Union Scientific Research Chemical-Pharmaceutical Institute in Moscow. In addition, studies were conducted at the Ukrainian Scientific Research Sanitary-Chemical Institute and in the Institute of Experimental and Clinical Oncology of the USSR Academy of Medical Sciences (now the Oncological Scientific Center of the USSR Academy of Medical Sciences).

These initial programs, plus others at the Chester Beatty Institute in Great Britain, Cancer Institute and University of Tokyo in Japan, Cancer Institute in Heidelberg, the National Cancer Institute in Budapest, and at research centers in other countries, generated great interest in the search for and development of new antitumor agents on a worldwide basis; thus chemotherapy programs were developed recently in many countries. The institution of the United States and USSR Medical Agreement has provided a unique opportunity for collaboration in preclinical cancer chemotherapy and the possibility for relating the results of such cooperative efforts to screening and drug development worldwide.

In 1970, L. F. Larionov (*2*) concluded: "I believe the time is ripe for international unification of screening procedures. Apparently it would be best to hold a special meeting either within the International Union Against Cancer or the World Health Organization."

At the VII International Congress of Chemotherapy in 1971 in Prague, a panel discussion was held on *The Predictability of Experimental Test Systems for Clinical Chemotherapy*. In a summary written by Goldin and Pujman (*3*), in a follow-up of L. F. Larionov's recommendation, they concluded that there would be considerable value in having an international conference on cancer chemotherapy screening. Goldin and Pujman stated, "At the panel in Prague there was general consensus that such a meeting should be held and that it would contribute definitely to progress in cancer chemotherapy." It was further recommended "At such a conference there could be discussion of international cooperation and the development of standards, choice of test systems and interchange of tumor materials, test agents and the results of drug evaluation. The relationship of preclinical screening and evaluation programs to the international clinical effort in cancer could receive prime attention."

With this stimulus, an International Conference on Screening Methodology for Anti-tumor Drugs sponsored by the WHO was held in Geneva in September 1974. At this conference were leading investigators in preclinical and clinical chemotherapy from most of the countries in which screening for anticancer activity is being conducted. The program of the International Conference on Screening Methodology for Anti-tumor Drugs encompassed important preclinical objectives of particular pertinence to the current collaborative program beween the United States and the Soviet Union.

A diversity of test systems for the screening and further evaluation of antitumor agents are used in various countries of the world, and a primary objective was to obtain a single composite listing and description of these test systems. The survey in Geneva of primary and secondary screens for the participating countries met this objective by providing a basis for the compilation and publication of the various test systems in the WHO Report "Description of Systems Used in Experimental Screening of Anti-Cancer Preparations in Sixteen Countries" (*4*). This included some detailed descriptions of the characteristics of the test systems, the identity of the principal investigators using these systems, and the types of compounds that have been identified as active by them. The listing encompasses both in vitro and in vivo test systems used as primary or secondary screens or for detailed drug evaluation and investigation.

A second important objective of the conference was the standardization of test systems. Such standardization encompasses animals and animal care, maintenance and propagation of tumor lines, tumor transplantation, quality control, preparation and administration of materials, selection of dosages, control and test group size, randomization of animals, and quantitative test evaluation, which includes appropriate experimental design, parameters, and criteria of responses. An ultimate objective evidently is

Abbreviations: WHO = World Health Organization; UICC = Union Internationale Contre le Cancer (International Union Against Cancer); OSC = Oncological Scientific Center; CICA = Committee on International Collaborative Activities.

[1] This Introduction was prepared by Abraham Goldin, Ira Kline, Zoya P. Sof'ina, and Anatoli B. Syrkin.

to establish worldwide protocols pertaining to drug testing, or at a minimum, to distribute a compilation of existing protocols from the various countries pertaining to animal breeding, standards of testing, and criteria of response.

With respect to the establishment of uniform worldwide standards for animals and drug evaluation, a specific objective of the conference was to focus attention on the 1) establishment of animal genetic centers for breeding and distribution of animals; 2) tumor cell banks for storage and distribution of tumor material; and 3) a centralized data bank for acquisition, storage, and distribution of screening and evaluation data to the various programs of the world, either directly or through regional data banks. Mechanisms were discussed and established for exchange of test materials, active drugs, significant findings, and collaborative publication. Exchange of active drugs at as early a date as possible was considered a most worthwhile objective, and steps were taken to implement such exchange.

At the Geneva meeting, participants considered that it would be most important to establish a common standardized reference screen, which if adopted in the various countries, would provide an important frame of reference and lead to uniformity in the interpretation of experimental data. The reference screen could be, but would not necessarily have to be, the first system in which the drug would be tested. However, it would be essential that as many compounds as possible and especially those active in other systems be tested in the reference screen and that the data be distributed universally, possibly through the data banks. The leukemia L1210 system was designated as a reference screen because of its highly quantitative characteristics and its good record of predictability of clinically active compounds. In their extensive retrospective analysis, Goldin et al. (*5*) emphasized that the L1210 system was capable of identifying successfully 16 of the 20 clinically established antitumor drugs, and of a more extensive list of 45 drugs showing activity in patient therapy it identified 33.

A most important preclinical objective pertains to the screens to be adopted. From the point of view of the preclinical chemotherapist, it is obviously unreasonable to expect that all screening programs should follow the same spectrum of test systems. On the other hand, the adoption of diversified screening systems has considerable merit. It was considered desirable that the workers in each laboratory use the standard reference screen agreed upon plus their specific spectrum of tumor systems. This in turn would result in the utilization of an extensive total number of test systems on an international basis and have the potential for detection of a maximum number of new and novel types of structures.

The Geneva conference participants emphasized the importance of communication and collaboration of both preclinical and clinical therapists on a worldwide basis.

The interest in collaborative chemotherapy is evidenced further by the number of recent important workshops held in various areas. One of these was a UICC workshop held in Budapest in April 1974 (*6*), which dealt with new approaches for chemotherapy models. In this workshop it became clear that new models, including xenografted human tumors in nude mice, could have considerable potential for large-scale primary screening and could be important for studies in tumor biology and immunology. Another UICC workshop was held on the subject "Drug Resistance and Selectivity in Cancer Chemotherapy" in Bratislava in July 1975 (*7*). This workshop was concerned with important specific questions related to the identification of target determinants of drug action and their potential as predictors of human tumor sensitivity or resistance to drugs. This was followed by a conference at the OSC in Moscow in September 1976 dealing with "Human Tumor Sampling for Biochemical Pharmacological Studies of Target Determinants of Drug Action" under the auspices of the UICC–CICA and the collaborative agreement between the United States and Soviet Union. The workshop served to focus attention in detail on specific problems pertaining to human tumor sampling for biochemical and pharmacologic investigations and led to a number of particular recommendations for further investigation. Arrangements were made for collaboration on pertinent problems between various centers represented at the workshop and also with researchers at other laboratories and institutes where specific expertise and interest is demonstrated.

In the USA–USSR Monograph "Methods of Development of New Anticancer Drugs" (*8*), several articles delineated various aspects of preclinical collaboration by the United States and Soviet Union in antitumor chemotherapy. Thus historically, it is a highly logical development for the United States and the Soviet Union to engage in a collaborative effort in tumor screening and drug evaluation, and steps were undertaken to implement this program.

In accordance with this Agreement, more than 150 drugs have been exchanged since the beginning of the program and are currently under investigation in both countries. The results of the studies with 30 American and 28 USSR drugs, a number of which are established as active clinically or are under clinical trial, have provided the possibility for detailed analysis of data collected in both countries. The analysis of this collective data is the primary objective of this Monograph. The authors have addressed the following problems:

1) Comparison of the data obtained by use of the same methodologic approaches with common and different tumor model systems.
2) Performance of an analysis of the experimental data in relation to clinical activity to establish the possibility for prospective prediction of antitumor activity of new drugs generally and against specific categories of tumor. For this purpose, biologic, biochemical, and specific mathematical approaches have been used; the data collected in each country and also common data were taken into account.
3) Use of the analysis in the improvement of screening systems in each country.

In addition to the presentation of the test data and

analyses, a listing of the drugs, their structures and properties, and descriptions of the tumor systems are included.

The results of this collaborative investigation may help to point the way to improvement of screening methodology and to future investigations and approaches for obtaining new effective drugs for patient therapy.

Chapter I: Drugs Included in the Joint Research Program of the United States and Soviet Union[1]

A: STRUCTURE, BIOLOGIC, AND BIOCHEMICAL CHARACTERISTICS OF ANTITUMOR DRUGS DEVELOPED IN THE UNITED STATES

The biochemical, pharmacologic, and other noteworthy biologic characteristics of the drugs from the United States are included.

Cyclophosphamide

The initial drug in this series, cyclophosphamide (NSC-26271), is inactive per se and must be biologically activated. The end product of the biologic activation of this agent was described by Rauen et al. (*9*) as the relatively stable compound *N*-β-chloroethyl-aziridine, which is formed spontaneously in vivo from *bis*-β-chloroethylamine. Brock (*10*) pointed out that cyclophosphamide is an inactive transport form, and in vivo this compound possessed the widest therapeutic range of several related alkylating agents studied. In pharmacologic studies done by Brock and Hohorst (*11*) in rats, the cytostatic activity in the serum was reached at 60 minutes. This level was strongly dose dependent and remained constant in the serum for approximately 1 to 2 hours, then it decreased to 30% after 4 hours, and finally disappeared after 24. The increase of serum cytostatic activity after oral or sc administration reached a maximum of only 50% of that observed after iv or ip injection.

Brock (*12*) also reported that after administration of this agent to mice, rats, and dogs, cytotoxic activity was observed in the serum and to a lesser extent in various blood-free organ extracts. High concentrations of the activation product were eliminated in the urine and in the bile. Depending on the dose, the maximum activity in the serum was reached as early as 15–30 minutes after administration and remained practically constant for 90–120 minutes. After 240 minutes, the activity fell to about 20–50% of the maximum value; after 24 hours it was not detectable. Liver sections incubated at 37° C in Ringer's solution containing glucose and agitated in a Warburg apparatus in the presence of oxygen caused an intense activation of cyclophosphamide. Such activation was absent in an atmosphere of nitrogen. Potel and Brock (*13*) showed that when cyclophosphamide was administered to rats, it inhibited specific antibody formation to a bacterial antigen stimulus and resulted in a reduction of leukocytes in the peripheral blood and plasma cells of the spleen; the effect is of limited duration.

1,3-Bis (2-chloroethyl)-1-nitrosourea

Schabel et al. (*14*) reported that 1,3-bis(2-chloroethyl)-1-nitrosourea (NSC-409962) had marked activity against ip inoculated leukemia L1210 when administered ip, sc, or orally. The nitrosoureas, of which BCNU seems to be one of the most highly active, were the first to possess an encouraging degree of activity against ic inoculated L1210 leukemia. When [^{14}C]BCNU was used, radioactive carbon was in all tissues examined, including the brain, and equal quantities were present in sensitive and resistant plasmacytomas of the hamster (*15*). DeVita et al. (*16*) studied the pharmacology of BCNU in man with [^{14}C]-labeled drug. Although radioactivity was excreted slowly in man and monkeys, it was eliminated rapidly in mice. Urinary excretion accounted for the major portion of the isotope, and as much as 10% was excreted as CO_2. The compound is degraded rapidly so that promptly after administration no intact drug is demonstrable. The high lipid solubility of this agent allows it to cross the blood–brain barrier rapidly. Wheeler and Bowdon (*17*) reported on the inhibition of de novo synthesis of purine ribonucleotides by high doses of the agent that resulted in the inhibition of the incorporation of carbon-14 from formate into purine of RNA and DNA.

1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea

The pharmacokinetics of CCNU (NSC-79037) was studied by Oliverio and co-workers (*18*) in mice, rats, dogs, and monkeys. They showed that the half-life of the initial phase for [^{14}C]-labeled CCNU is approximately 5 minutes, whereas the second phase extends over 1 hour. During 6 hours after iv injection into dogs, radioactivity in the CSF exceeded that of the plasma threefold. After biotransformation, the drug is primarily excreted by the kidneys; within the first 24 hours, it is completely excreted in rodents and monkeys, but is more protracted in dogs. Henry et al. (*19*) performed hepatotoxicity studies

Abbreviations: BCNU = 1,3-bis(2-chloroethyl)-1-nitrosourea; ic = intracerebral(ly); CCNU = 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea; CSF = cerebral spinal fluid; 5-FU = 5-fluorouracil; ara-C = cytosine arabinoside; *cis*-PT(II) = *cis*-platinum(II) diamminedichloride; LD50 = mean lethal dose; CNS = central nervous system; AMSA = 4′-(9-acridinylamino)-methanesulfon-*m*-anisidide; PCNU = 1-(2-chloroethyl)-(2,6-3-dioxo-3-piperidyl)-1-nitrosourea; Me-CCNU = 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea; DTIC = dacarbazine; MTD = maximum tolerable dose; MNU = methylnitrosourea.

[1] This chapter was prepared by I. Kline, I. S. Levi, Y. N. Shkodinskaya, A. K. Belousova, and N. D. Lagova.

with CCNU in dogs and demonstrated toxicity following oral administration of a single dose. Levin and associates (*20*) demonstrated the antitumor activity of CCNU against ependymoblastoma, glioma 26, and glioma 261 of mice. They also studied the uptake and distribution of [^{14}C]CCNU in intracerebral and subcutaneous tumors. The studies showed that the radioactive drug was taken up by the normal brain adjacent to the tumor, as well as by distant normal brain tissue, and that the parent drug had relatively constant tissue : plasma ratios. Cheng et al. (*21*) conducted extensive studies with [^{14}C]CCNU on its binding to proteins and nucleic acids. These investigators reported that the carcinostatic activity of this drug reflects a modification of the cellular proteins as well as of nucleic acids. Wheeler and co-workers (*22*), in considering the biochemical therapeutic properties of alkylating agents, indicated that a nitrosourea having optimal therapeutic properties would have low carbamoylating activity, low chemical stability, high alkylating activity, and a distribution coefficient falling at the upper end of the range for the compounds included in their studies.

Uracil Mustard

Lyttle and Petering (*23*) reported on some of the biologic characteristics of uracil mustard (NSC-34462) in the Walker carcinosarcoma 256. These investigators showed that this compound had a marked degree of activity in this tumor system and that it was more effective when given intermittently rather than daily. They also noted that the usual side effects of nitrogen mustards were absent. Brunk and Cavanaugh (*24*) studied the distribution of radioactive uracil mustard in rats and determined drug levels in the livers, kidneys, spleens, and small intestines. Of the injected radioactivity, 2.6% was localized in the liver at 30 minutes; the level gradually declined to 0.26% at 96 hours.

Imidazole Mustard (TIC-mustard)

Imidazole mustard (NSC-82196) is an unstable compound easily convertible to an isomeric transformation product. With appropriate precautions, however, this compound may be prepared in good yield with little of the transformation product as a contaminant. It may be stored for long periods at low temperatures (*25*). Vogel et al. (*26*), using [^{14}C]imidazole mustard in their studies to elucidate the in vitro stability of this compound and its physiologic disposition including absorption, excretion, and metabolism in mice and dogs, reported the plasma half-life in dogs to be 2 hours after iv administration, but penetration of the blood–brain barrier was negligible. Gastrointestinal absorption after oral administration was poor and erratic. The primary route of excretion of absorbed drug was renal in both species, and more than 60% of the drug was excreted in the urine by dogs within 6 hours after iv administration.

Streptozotocin

Streptozotocin (NSC–85998), an antibiotic extracted from *Streptomyces achromogenes* and prepared in highly purified form, is a highly effective cytotoxic agent for pancreatic β-cells. Whereas the cytotoxic properties of streptozotocin resemble those of alloxan, its specificity is considerably greater, as demonstrated by the wide margin between a diabetogenic dose and general toxicity (*27*). Evans et al. (*28*) reported on the persistent glycosuria produced by streptozotocin and elaborated further upon the mechanism of the diabetogenic action of this compound. Schein and Loftus (*29*) studied the biochemical properties of streptozotocin and noted that after a single diabetogenic iv dose, this agent produced a 24-hour depression of oxidized and reduced nicotinamide adenine dinucleotide content in mouse liver. These investigators suggested that streptozotocin inhibited the synthesis of pyridine nucleotides. Bhuyan (*30*) studied the biochemical properties of streptozotocin in in vitro systems and reported that this agent inhibited the incorporation of precursors into DNA to a greater degree than into RNA or protein. Bhuyan et al. (*31*) described the pharmacologic characteristics of streptozotocin and pointed out that streptozotocin levels in plasma decreased rapidly, with a half-life of 10 to 15 minutes; however, the levels were maintained for a longer period in the tissues. Streptozotocin was excreted so rapidly in the urine that 72% of the total radioactive injected material could be accounted for in the urine after 4 hours (*31*). Rakieten and associates (*32*), who administered single diabetogenic doses of pure streptozotocin to rats and induced renal tumors in 29% of these animals, discovered that the tumorigenic properties of streptozotocin may be related to the *N*-nitrosoalkane end of the molecule or to the in vivo release of this group as diazomethane.

Hexamethylmelamine

Hexamethylmelamine (NSC-13875) has been studied by Worzalla et al. (*33*) with respect to metabolism and physiologic distribution in patients and in rats. Following administration of the radioactive drug orally to patients, respiratory [^{14}C]O_2 was detected within 1 hour, and the level accumulated to 9% of the administered dose in 6 hours. After 72 hours, 29% of the radioactivity was recovered in the urine and 0.5% in the feces. In rats, oral and ip administration of the radioactive drug led to the recovery of 13 and 30%, respectively, of the dose of [^{14}C]O_2 in 24 hours. At 72 hours after oral administration of labeled drug, 58% of the radioactivity was recovered as follows: 16% as [^{14}C]O_2, 38% in the urine, and 4% in the feces. In the same interval, 80% of the ip dose was recovered as follows: 33 as [^{14}C]O_2; 42 in the urine; and 5 in the feces. Worzalla and his associates noted that demethylation appears to be significant in the metabolism of hexamethylmelamine in man and in rats. Lake et al. (*34*), after their investigation of the mechanism of action of hexamethylmelamine, suggested that the *presence* of a methyl group rather than the *number* of methyl groups was the determining factor in the antitumor activity of the methylmelamines.

5-Fluorouracil

Bosch and associates (*35*) in a report on various biochemical properties of 5-FU (NSC-19893) and other related fluorinated pyrimidines showed that these compounds inhibited the incorporation of [^{14}C]-labeled formate into DNA thymine, and with the exception of 5-fluoro-2′-deoxyuridine, inhibited the incorporation of uracil into RNA. They concluded that fluorinated pyrimidines inhibit the metabolic methylation of deoxyuridine monophosphate to thymidine monophosphate. Chaudhuri et al. (*36*) used ([^{14}C]-labeled 5-FU to follow the excretion, distribution, and metabolism of this agent in mice and in patients with cancer. The compound was excreted rapidly and unchanged in the urine shortly after injection. They also reported that 5-fluorouridine nucleotides at the mono, di, and triphosphate levels were incorporated into RNA, but not into DNA, in mouse liver, spleen, sarcoma 180, Ehrlich ascites carcinoma, and human metastatic carcinoma.

Cyclocytidine

Cyclocytidine (NSC-145668) has been reported (*37*) to be a more potent and less toxic antineoplastic agent than the parent compound cytosine arabinoside (ara-C). The anhydronucleoside interrupted tumor growth in a stepwise manner, possibly reflecting its slow hydrolysis to arabinosylcytosine (*37*). Their observation suggested that cyclocytidine is a depot form of arabinosylcytosine. Ho (*38*) pointed out that although this compound is a schedule-independent antitumor agent in various experimental systems, ara-C is schedule dependent. Cyclocytidine is not deaminated by the abundant deaminase in human liver and mouse kidney. In further studies on other biochemical properties of cyclocytidine, Ho (*39*) showed in in vivo systems that cyclocytidine possessed a lesser but longer lasting effect than ara-C. From studies in mice and dogs, it was suggested that cyclocytidine is hydrolyzed to arabinosylcytosine in vivo and may thus serve as a reservoir of the latter. Cyclocytidine is a weak inhibitor of DNA synthesis in mouse leukemia L1210 cells according to Kessel's (*40*) research. This compound is gradually hydrolyzed, apparently by a nonenzymatic process, to ara-C in the extracellular space, and rapid uptake of the latter compound resulted in progressive inhibition of DNA synthesis. (*40*).

Hirayama et al. (*41*) performed distribution assays of cyclocytidine on the urine and feces of monkeys, dogs, and rats. The administered cyclocytidine showed a half-life of 22 minutes in the plasma of dogs and monkeys, whereas that of 1-β-D-arabinofuranosylcytosine hydrochloride (ara-C) was in the plasma of dogs 47 minutes and less than 5 in the plasma of monkeys because of the rapid deamination of the compound. These workers pointed out that the rate of distribution and elimination of cyclocytidine after iv administration is not affected by the presence of cytidine deaminase in the plasma and tissues. When Ho et al. (*42*) studied the clinical pharmacology of cyclocytidine, they detected two metabolites of 2-[^{14}C]-cyclocytidine in the plasma and urine, the hydrolytic product ara-C and its deaminated product ara-U, in cancer patients. Eighty percent of the dose was found in the urine in 24 hours: 70% as cyclocytidine and 10% as ara-C and ara-U. The plasma disappearance curve of ara-C is linear, and the estimated half-life is 8 hours.

Ho and co-workers (*43*) performed additional pharmacologic studies of cyclocytidine with dogs. After the drug was administered, the two metabolites were again found in the plasma and urine. The urinary excretion of cyclocytidine was rapid, and 5 hours after parental administration, 60% of the drug was excreted, with 45% as cyclocytidine, 10% as ara-C, and 5% as ara-U. In contrast, after similar administration of ara-C, 45% of the drug is eliminated, 33% as ara-C and 12% as ara-U.

5-Azacytidine

Čihak and Vesely (*44*) conducted biochemical studies with 5-azacytidine (NSC-102816) in regenerating rat liver. It was proposed that the inhibitory effect and the changes in the polyribosome pattern are due to the incorporation of 5-azacytidine into newly synthesized RNA. Levitan and Webb (*45*) reported that 5-azacytidine also caused a breakdown of hepatic polyribosomes. In addition, 5-azacytidine prevented the inactivation of tyrosine transaminase, but not that of tryptophan pyrrolase, which normally occurs after an increase in hormone. In cell culture research with the agent and L1210 leukemia cells performed by Li et al. (*46*), 5-azacytidine inhibited mitosis, and this inhibition was correlated with that of DNA synthesis. 5-Azacytidine predominantly killed cells in the S-phase. In addition, this agent caused considerable chromosome damage to the L1210 cells in culture. Chabner et al. (*47*) showed that 5-azacytidine undergoes enzymatic deamination by peripheral human leukemia leukocytes. Increased levels of the enzyme cytidine deaminase may reduce the effectiveness of 5-azacytidine in the treatment of human leukemia. That inhibitors of pyrimidine deamination, such as tetrahydrouridine, are helpful in preventing catabolism of this antineoplastic agent is possible.

***cis*-Platinum (II) Diamminedichloride**

The inhibitory effect of *cis*-platinum compounds was studied in vitro with the use of human amnion cells (*48*). Those compounds that inhibited tumor most effectively also inhibited DNA synthesis selectively and [^{3}H]dThd incorporation more rapidly than [^{3}H]uridine or [^{3}H]leucine incorporation. The binding mechanism of *cis*-Pt (II) (NSC-117875) to DNA (*49*) and its toxicologic effects in dogs, monkeys, and mice (*50*) were investigated; dose-related morbidity generally was demonstrated within 5 to 7 days after administration of the compound. Toxic signs included severe hemorrhagic enterocolitis, hypocellularity of the bone marrow and lymphoid tissues, and marked renal lesions. Occasionally, pancreatitis was observed in dogs and myocarditis in monkeys.

In a clinical study by DeConti et al. (*51*), the half-life of *cis*-Pt (II) was 25 to 49 minutes, with a secondary phase that ranged from 58 to 73 hours. Urinary excre-

tion was incomplete with only 27 to 45% of the radioactive drug eliminated in the first 5 days. Renal impairment was the dose-limiting toxicity in the single-dose escalation scheme used.

Stadnicki et al. (*52*) found that transient hearing loss occurred in the monkey treated with the largest dose administered and in 1 of 3 animals treated at a lower dose. These findings indicated that when *cis*-Pt (II) was given in a treatment regimen that caused more severe organ toxicity, it caused less severe ototoxicity than neomycin sulfate.

Gallium Nitrate

The toxicity and antitumor activity of various salts including gallium nitrate (NSC-15200) were reported by Hart and Adamson (*53*). Gallium ranked third with respect to toxicity in experimental animals in an order of four inorganic salt–metal complexes. All four metals exhibited antitumor activity, but when the tumor was inoculated by a route different from that of the drug, only gallium inhibited tumor growth.

Guanazole

When Brockman et al. (*54*) studied the biochemical properties of guanazole (NSC-1895), they found that it inhibited the incorporation of adenine, hypoxanthine, and uridine into DNA to a much greater extent than into RNA in L1210 leukemia cells in vivo. Similar results were obtained when they used human epidermoid carcinoma cells in culture; guanazole inhibited the reduction of ribonucleotides to deoxyribonucleotides. Hahn and Adamson (*55*), in their paper on the properties of guanazole, stated that the compound was active against leukemia L1210 implanted ic. They also observed that a variant of leukemia L1210 made resistant to guanazole was not cross-resistant to dichloromethotrexate, BCNU, and ara-C. An investigation by Vick and Herman (*56*) on the effect of guanazole on the heart and blood pressure of dogs revealed that this agent produced a sharp drop in arterial blood pressure, an increase in right ventricular pressure, a slight decrease in heart rate, and a rise in central and portal venous pressures. These changes were transient, lasting from 5 to 10 minutes, and could be partially ameliorated by prior treatment with antihistamine, antiserotonin, and adrenergic blocking drugs. After Musa et al. (*57*) administered [^{14}C]guanazole orally to rats, the blood levels of the labeled drug peaked at about 1 hour after dosing and declined in two distinct phases. The half-life of the slower phase was 3.2 hours. Tissue distribution of the labeled material was observed 90 minutes after dosing and showed the highest concentration of the drug in the bladder and the lowest in abdominal fat.

Ellipticine

Bhuyan and co-workers (*58*) investigated the biochemical characteristics of ellipticine (NSC-71795) in cell culture of a Chinese hamster fibroblast line and determined that it inhibited DNA and RNA synthesis more than protein synthesis and also interacted with DNA to cause severe chromosomal aberrations. Li and Cowie (*59*) reported that ellipticine significantly inhibited DNA, RNA, and protein synthesis and the inhibition was not reversible by the removal of the drug in cultured L1210 cells. Ellipticine bound preferentially to helical DNA by intercalation, and the strength of the binding was substantially greater than that of proflavin (*60*). Hardesty and associates (*61*) observed distribution of ellipticine in mice after the agent was administered in solution and as a suspension given orally or ip; the highest and lowest tissue levels occurred after its administration ip in solution and suspension, respectively. The major portion of this drug was present in the feces; only trace amounts were present in the urine. Although ellipticine decreased the blood pressure and the heart rate of monkeys, the carotid artery blood flow increased (*62*). Herman and his co-workers (*62*) also found that ellipticine produced immediate and marked hemolysis in anesthetized monkeys.

3-Tritylthio-L-alanine

In a report on the pharmacokinetics of 3′tritylthio-L-alanine (NSC-83265), Coffey et al. (*63*) stated that the rat absorbed this drug (which had a half-life of 20 hr) slowly and excreted it rapidly, chiefly in the bile. With a half-life of about 81 hours in dogs and monkeys, the compound showed rapid first-order absorption and slow excretion, mainly in the urine. The monkey excreted more in the urine than the dog. The main site of drug concentration in the tissues of the three species was the liver, with appreciable concentrations also in the kidney of the monkey.

Kessel et al. (*64*), when working on the biosynthesis of L1210 cells in culture, detected that 3-tritylthio-L-alanine interfered with the incorporation of precursors into nucleic acid and protein and caused disorganization of cell membranes.

Inosine Diglycolaldehyde

Inosine diglycolaldehyde (NSC-118994) inhibited ribonucleotide reductase in cell-free extracts from Ehrlich tumor cells (*65*). Cysyk and Adamson (*66, 67*) reported that the excretion of this drug in the urine of mice, rats, and monkeys was rapid, with 35 to 59% eliminated during the first 3 hours and a total of 58 to 68% excreted in 24 hours.

Dichloroallyl Lawsone

Dichloroallyl lawsone (NSC-126771) inhibited succinoxidase according to Iwamoto et al. (*68*), who researched the drug. With reference to its pharmacokinetics, Chadwick et al. (*69*) stated that, although dichloroallyl lawsone had a higher therapeutic index than the parent compound lapachol, the half-times of absorption of the two drugs were similar. Also, concentration-time curves for this agent were greater than that for the parent compound. In earlier work, Chadwick and Chang (*70*) found that

the concentration of dichloroallyl lawsone in the plasma and heart was approximately 10 times higher at 2 minutes after injection than after oral administration.

Indicine-*N*-oxide

The toxic doses of indicine-*N*-oxide (NSC-132319) were determined in mice, dogs, and monkeys by Castles et al. (*71*), who also described hematologic changes, bone marrow depression, and gastrointestinal toxicity. The lethality of a 1,200-mg/kg dose was discovered when this agent was given iv; an iv dose of 300–600 mg/kg was toxic for beagle dogs (*72*).

Coralyne Sulfoacetate

Studies on the preclinical toxicology of coralyne sulfoacetate (NSC-154890) were performed by Castles and his associates (*73*). In mice and hamsters given iv injections, the LD50 of this drug was approximately 222 mg/kg. In dogs, single iv doses of 75 or 37.5 mg/kg caused death in 10 and 66 days, respectively. At the lower dose, anorexia occurred in 44 days and was followed by marked body weight loss of approximately 57% and death by day 67.

α-2′-Deoxythioguanosine

LePage et al (*74*), in investigations of the biochemical carcinostatic properties of α- and β-2′-deoxythioguanosine (NSC-71851) found that, although the β-anomer, thioguanine riboside, and thioguanine appeared to be of approximately equal toxicity on a molarity basis, the α-anomer was actually much less toxic. Ten years later, Henry and Didomenico (*75*) studied the preclinical toxicology of this agent in dogs and monkeys; it was characterized initially by the development of emesis, diarrhea and anorexia, anemia, and leukopenia. Gastrointestinal toxicity and significant thrombocytopenia were present only at higher levels. With extended treatment, the bone marrow components were depressed, and this condition was not reversed during the rest period after drug treatment.

3-Deazauridine

Using extracts of lekemia L1210 cells to examine the mechanism of action of 3-deazauridine (NSC-126849), McPartland and co-workers (*76*) suggested that deazauridine exerted its growth inhibitory activity by interfering with the activity of cytidine triphosphate synthetase. Administration of testosterone, either concomitantly with the drug or in depot form 5 days before drug treatment, prevented or reduced both weight loss and mortality (*77*). Histopathologic changes produced in the intestinal epithelium by 3-deazauridine were alleviated by the administration of testosterone.

6-Selenoguanosine

Ross et al. (*78*), after studying the biochemical properties of 6-selenoguanosine (NSC-137679), reported that guanine, 6-thioguanine, and 6-selenoguanosine showed comparable substrate activity, whereas azaguanine was a much poorer substrate for hypoxanthine-guanine phosphoribosyl transferase in mouse sarcoma 180 cells.

Townsend's Nucleoside Derivative

Plagemann (*79*) investigated the biochemical properties of Townsend's nucleoside [1,4,5,6,8-pentazaacenaphthylene-3-amino-1,5-dihydro-5-methyl-(5-^{14}C)-1-β-D-ribofuranosyl] (NSC-154020). Within two hours this compound completely inhibited the incorporation of [^{14}C]-formate into nucleotides and nucleic acids of Novikoff hepatoma cells. However, the inhibition of de novo synthesis of purines and pyrimidines was not the only toxic effect of this agent because high concentrations of uridine, adenine, guanine, and hypoxanthine, either alone or combined, failed to prevent the inhibition of cell replication by Townsend's nucleoside. Bennett and associates (*80*) reported that it was degraded to a single compound characteristic of a 5′-monophosphate. The nucleoside inhibited the incorporation of [^{14}C]formate and [^{14}C]hypoxanthine into polynucleotides. Using [^{14}C]-tagged material during investigations with dogs, Friedman et al. (*81*) found that the biologic half-life of this drug was 19 minutes. Also, studies on excretion showed that within 5 hours only about 5% of the labeled material was excreted in the urine, of which over 50% is the unchanged nucleoside; the remainder consisted of several metabolites. An unusual feature of this compound was that 54% of the administered dose was excreted in the bile in high concentrations.

ICRF-187 (Soluble Form of ICRF-159)

To relate toxicity and therapeutic efficacy to dose better and to facilitate pharmacologic studies, Venditti and Wolpert-DeFillippes (*82*) reported on a soluble parenteral formulation of ICRF-159 (ICRF-187; NSC-169780). The water-soluble material was four times as soluble as the racemic mixture. Antitumor research with the soluble product indicated that it was equivalent in activity to ICRF-159 in the L1210, B16, and LL mouse tumor systems.

Spirohydantoin Mustard

Peng et al. (*83*) reported that spirohydantoin mustard (NSC-172112), prepared as a nitrogen mustard carrier for CNS antitumor evaluation, produced cures repeatedly in the murine ependymoblastoma brain tumor system. This rationally designed CNS-directed nitrogen mustard has the ability to cross-link with DNA in the intracerebral rat glioma 9L and in bone marrow (*84*).

Quinolinium Derivative

Atwell and Cain's (*85*) data on a series of quinolinium (NSC-176319) compounds indicated that the 7-NO_2 quinoline congeners had high activity, whereas all 6-NO_2 variants proved inactive.

Chlorozotocin

Against Chinese hamster cells in vitro, chlorozotocin (NSC-178248) was approximately 40 times more toxic for noncycling cells and 20 times more so for cycling cells in comparison with streptozotocin (*86*). When Anderson et al. (*87*) studied the effect of this agent against mouse leukemia L1210, it produced no significant depression in either normal bone marrow DNA synthesis or peripheral neutrophil count. In contrast, it produced greater than a 90% inhibition of DNA synthesis in leukemia ascites cells. In their findings on additional structure–activity studies of nitrosourea derivatives, Schein and co-workers (*88*) showed that chlorozotocin produced only minor degrees of inhibition in mouse and human bone marrow DNA synthesis as compared with BCNU.

Cain's Acridine Derivative

Cysyk and Adamson (*89*) reported on the pharmacologic properties of Cain's acridine derivative [acridinyl anisidide, AMSA; (NSC-249992)]. Using radioactively tagged material, they found that the compound is eliminated rapidly in the bile and more than half of the administered dose was excreted in the first 2 hours. Chromatographic analysis of the bile indicated that nearly all of the radioactivity was associated with one metabolite. More of the [^{14}C]-labeled material was in the liver, bladder, and spleen. These investigators also determined that this compound interacts strongly with DNA. In additional studies of the biochemical properties of acridine derivatives, Waring (*90*) showed that they bind to DNA by intercalation.

1-(2-Chloroethyl)-3-(2,6-dioxo-3-piperidyl)-1-nitrosourea

The effectiveness of PCNU (NSC-95466) and other nitrosoureas in rats inoculated ic with sarcoma cells was investigated by Levin and Kabra (*91*). Their studies revealed that PCNU had greater alykylating activity, lower carbamoylating activity, and superior antitumor activity compared with CCNU, BCNU, and Me-CCNU. Based on these findings, they suggested that PCNU should be evaluated further as a potentially useful chemotherapeutic agent against brain tumors.

5-(3,3-Dimethyl-1-triazeno)-imidazole-4-carboxamide (Dacarbazine)

Pharmacologic studies with DTIC (NSC-45388) conducted by Loo et al. (*92*) indicated that plasma clearance of the drug in the dog was rapid, with a half-life of about 36 minutes. Excretion was complete in 6 hours, at which time the cumulative excretion was 17% of the injected dose; the drug appeared in the CSF 10 minutes after injection. When administered iv to man, the plasma clearance of DTIC was similar to that seen in the dog, with a plasma half-life of 35 minutes, but when given orally, the cumulative excretion of DTIC was variable and, on the average, 19% of the dose was in the urine in 6 hours. These results suggested that the gastrointestinal absorption of DTIC was slow, incomplete, and variable. Additional pharmacologic studies with DTIC were done by Householder and Loo (*93*) with mice, in which they observed that after an ip injection of the drug, 56% of the radioactive material was in the carcass at 15 minutes and that it diminished to 4.7% at 24 hours. Organ distribution of the radioactive drug in tumor-bearing mice was markedly different than in normal animals. The cumulative urinary excretion of radioactivity after iv injection of the labeled drug was 40–66% in 5 hours, and 36–84% of this represented unchanged DTIC.

In humans, the dog, and the mouse, the major metabolite of DTIC was 5-aminoimidazole-4-carboxamide. Gerulath and Loo (*94*) observed that DTIC was more lethal in the presence of light than in the dark to Chinese hamster ovary cells than to human melanoma cells in vitro. They also pointed out that when light was excluded, an alternative pathway of decomposition was followed, and 5-aminoimidazole-4-carboxamide and a methyl carbonium ion were formed, which then interacted with cellular DNA.

The structure and solubility characteristics of the USA drugs included in the joint study are presented in table 1.

B: STRUCTURE, BIOLOGIC, AND BIOCHEMICAL CHARACTERISTICS OF SOVIET ANTITUMOR DRUGS

At the end of the 1940's, L. F. Larionov advanced the idea of the selective synthesis of alkylating agents in which metabolites and biologically active substances are used as carriers of cytotoxic "warheads" (*120, 121*).

Dopan

Dopan (NSC-44629), one of the first representatives of this type of "alkylating metabolite" (*122*) is active against a number of transplantable and inducible tumors of mice, rats, and rabbits and is capable of evoking total regression of some of them. Its toxic effect is manifested in reversible suppression of hematopoiesis, particularly granulocytopoiesis.

[^{14}C]Dopan administered orally to rats is detected in all tissues and organs, especially in the bone marrow and liver, and is retained there for an extensive period (*123*).

The antitumor effect of dopan may be reduced by prior administration of large doses of the methylpyrimidines, methyluracil and pentoxyl (*124*), which suggests that a pyrimidine carrier of chlorethylamine groups may contribute to the realization of antitumor effect.

Twenty-four hours after the administration to rats with sarcoma 45 at an MTD, dopan elicits marked reduction of DNA synthesis in the liver, spleen, and bone marrow. In normal tissues, the impaired synthesis is fully restored in 72 hours, whereas in the tumor, there is only partial restoration at this time.

On the basis of the depth of suppression of DNA and RNA synthesis in tumor cells and the capacity to induce the appearance of cross-links and breaks in DNA molecules, dopan can be classified as a potent alkylating agent.

TABLE 1.—*Drugs from the United States included in the program of American–Soviet research*

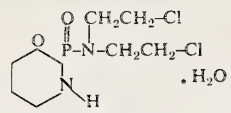
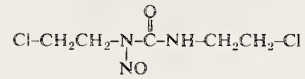
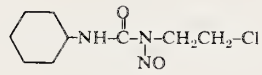
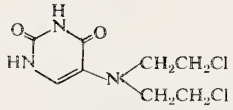
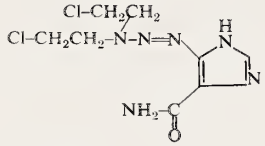
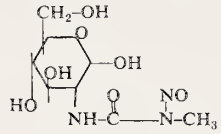
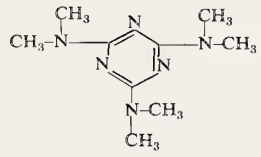
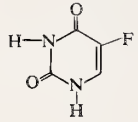
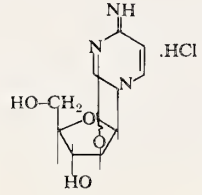
NSC No.	Compound name	Structural formula	Characteristics of drug	References
26271	Cyclophosphamide		Soluble in water Stability, 6 days (refrigeration) Vehicle: saline Log: $P = +0.629 \pm 0.040$	(*95*)
409962	1,3-Bis(2-chloroethyl)-1-nitrosourea (BCNU)		Solubility, 4.25 mg in 1 ml ethanol Stability, 12% decomposition at 6 hr Vehicles: saline and alcohol Log: $P = +1.532 \pm 0.018$	(*14*)
79037	1-3 (2-Chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU)		Solubility: <0.5 mg/ml in water Stability: solubility of 4.5/100 ml, 6 hr Vehicle: Klucel Log: $P = 2.828 \pm 0.023$	(*96*)
34462	5-Bis(2-chloroethyl)-aminouracil (Uracil mustard or Nordopan		Insoluble in water Soluble in dilute acid Stability, hydrolyzes in water Vehicle: CMC	(*97*)
82196	5-[3,3-Bis(2-chloroethyl)-1-triazeno]-imidazole-4-carboxamide (Imidazole mustard; TIC-mustard)		Solubility, 5 mg/100 ml water Stability, solution decomposes (HCl) in 30 min Vehicle: Klucel	(*98*)
85998	2-Deoxy-2-(3-methyl-3-nitrosoureido)-D-glucopyranose (Streptozotocin)		Solubility, 20 mg/ml water Stability, buffered citrate solution stable for 8 hr Vehicle: saline	(*99*)
13875	2,4,6-Tris (dimethylamino)-*s*-triazine (Hexamethylmelamine)		Solubility, 0.92 mg/ml Stable in bulk and solution Vehicle: Klucel Log: $P = +2.524 \pm 0.007$	(*100*)
19893	5-Fluorouracil (5-FU)		Soluble in water Stable Vehicle: saline Log: $P = -0.982 \pm 0.019$	(*101*)
145668	Cyclocytidine		Solubility, 200 mg/ml in water Stability, 1% solution in water for 24 hr Log: $P = -2.263 \pm 0.023$	(*102*)

TABLE 1.—*Drugs from the United States included in the program of American–Soviet research (continued)*

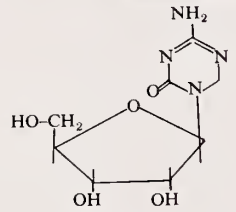
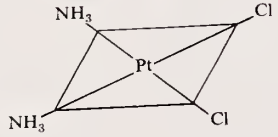
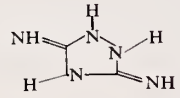
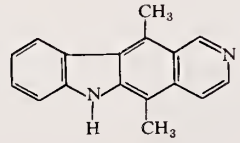
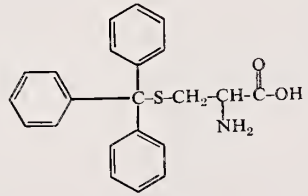
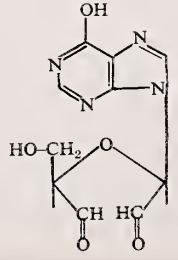
NSC No.	Compound name	Structural formula	Characteristics of drug	References
102816	5-Azacytidine		Solubility, 14 mg/ml in water Stability, 9% decomposition in solution in 24 hr, 30 days in bulk at 60° C Vehicle: saline	(*103*)
119875	*cis*-Platinum(II) diamminedichloride		Solubility, 1 mg/ml in water Vehicle: saline	(*104*)
15200	Gallium nitrate	$Ca(NO_3)_3$	Solubility, 650 mg/ml in water Stable Vehicle: saline	(*105*)
1895	Guanazole		Solubility, 200 mg/ml in water Stable at room temperature for 24 hr Vehicle: saline Log: $P = -1.610 \pm 0.011$	(*106*)
71795	Ellipticine		Solubility, <0.01 mg/ml in water Stability Bulk, no decomposition after 60 days at room temperature Vehicle: saline and Tween-80 Log: $P = +4.805 \pm 0.044$	(*107*)
83265	3-Tritylthio-L-alanine (*s*-trityl-L-cysteine)		Solubility, <0.02 mg/ml in water Stability Bulk, no decomposition after 30 days Solution, no decomposition in saline Vehicle: saline Log: $P = 1.046 \pm 0.018$	(*108*)
118994	Inosine diglycolaldehyde		Solubility, 500 mg/ml in water Stability Bulk, no decomposition at 60° C after 30 days Solution, no decomposition after 24 hr Vehicle: saline Log: $P = -2.114 \pm 0.004$	(*65*)

TABLE 1.—*Drugs from the United States included in the program of American–Soviet research (continued)*

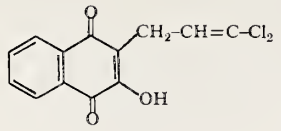
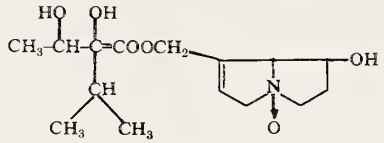
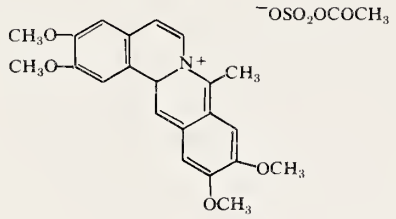
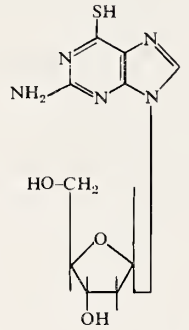
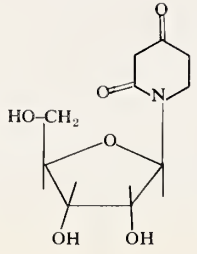
NSC No.	Compound name	Structural formula	Characteristics of drug	References
126771	Dichloroallyl lawsone		Solubility, 1 mg/ml in water Stability Bulk, no decomposition at 60° C for 30 days Solution, no decomposition at room temperature for 24 hr Vehicle: Klucel Log: $P = +3.103 \pm 0.004$	(*109*)
132319	Indicine-*N*-oxide		Solubility, 100 mg/ml in water Stability Bulk, 5% decomposition after 30 days at room temperature Solution, no decomposition after 24 hr Vehicle: saline Log: $P = -1.525 \pm 0.035$	(*110*)
154890	Coralyne sulfoacetate		Solubility, 6.3 mg/ml in water Stability Bulk, 1% decomposition after 30 days Solution, 3% decomposition after 24 hr at room temperature Vehicle: saline Log: $P = -0.859 \pm 0.046$	(*111*)
71851	α-2′-Deoxythioguanosine (α-TGdR)		Solubility, 7.1 mg/ml in water Stability Bulk, no decomposition at 60° C for 28 days Solution, no decomposition at room temperature Vehicle: saline and Tween-80 Log: $P = -0.851 \pm 0.036$	(*112*)
126849	3-Deazauridine		Solution, 18 mg/ml in water Stability Bulk, no decomposition at 60° C for 30 days Solution, no decomposition at room temperature for 24 hr Log: $P = -2.280 \pm 0.008$	(*113*)

TABLE 1.—*Drugs from the United States included in the program of American–Soviet research (continued)*

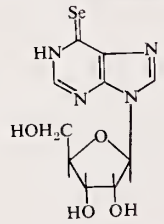
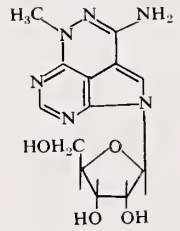
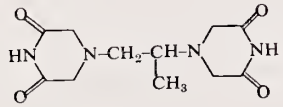
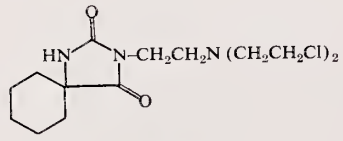
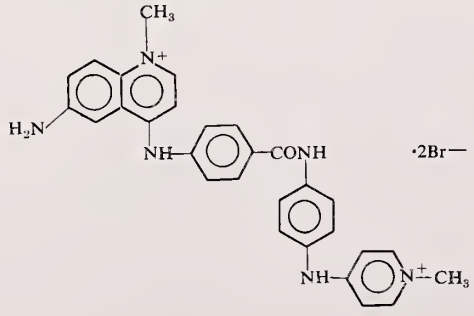
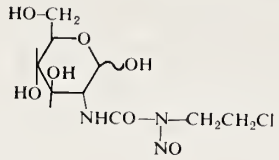
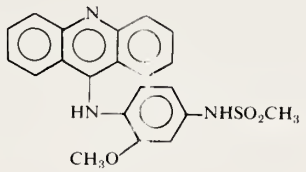
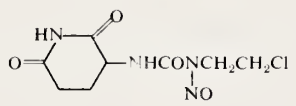
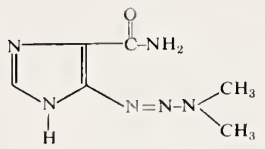
NSC No.	Compound name	Structural formula	Characteristics of drug	References
137679	6-Selenoguanosine		Impurity problem affects solubility and stability	(*114*)
154020	1,4,5,6,8-Pentaazaacenapthylene-3-amino,1,5-dihydro-5-methyl-1-β-D-ribofuranosyl (Townsend's nucleoside derivative; TCN)		Insoluble in water Soluble in 0.1 N HCl (20 mg/ml) Vehicle: saline and Klucel	(*115*)
169780	4,4′-(1-Methyl-1,2-ethanediyl)bis-2,6-piperazinedione (+) (ICRF-187; soluble form of ICRF-159)		Solubility, 10–12 mg/ml in water Stability Bulk, <1% decomposition at 60° C after 7 days Solution, 42% decomposition after 6 days at 28° C Vehicle: water	Creighton AM: Personal communication
172112	Spirohydantoin mustard		Solubility, <0.01 mg/ml in water Stability Bulk, stable for 30 days at 60° C Saturated solution in DMA had a half-life of 30–60 min Vehicle: saline and Tween-80	(*83*)
176319	6-Amino-1-methyl-4-[[[[[[(1-methyl pyridinium-4-yl)-amino]phenyl] amino]-carbonyl]phenyl]amino]-quinolinium dibromide (quinoline derivative)		Solubility, 8.3 mg/ml in water Stability Bulk, no decomposition at 60° C for 30 days Solution, 0.2% aqueous, no decomposition after 24 hr Vehicle: Klucel	(*85*)

TABLE 1.—*Drugs from the United States included in the program of American–Soviet research (continued)*

NSC No.	Compound name	Structural formula	Characteristics of drug	References
178248	Chlorozotocin		Solubility, <18 mg/ml in water Stability Bulk, at 60° C considerable decomposition after 24 hr Solution, 40% decomposition at room temperature at 25 hr Vehicle: saline Log: $P = -1.019 \pm 0.017$	(*116*)
249992	4′-(9-Acridinylamino)-methanesulfon-*m*-anisidide (Cain's acridine derivative; AMSA)		Soluble, 1 mg/ml in water Stable in water for 4 days Vehicle: saline and alcohol	(*117*)
95466	1-(2-Chloroethyl)-3-(2,6-dioxo-3-piperidyl)-1-nitrosourea (PCNU)		Solubility, <1 mg/ml in water Stability, solution decomposed 38% after 24 hr Vehicle: saline and Tween-80 Log: $P = +0.374 \pm 0.012$	(*118*)
45388	5-(3,3-Dimethyl-1-triazeno)-imidazole-4-carboxamide (DTIC; dacarbazine)		Solubility, 1.0 mg/ml in water, 12.0 mg/ml in 0.1 N HCl Stability in citric acid, mannitol, and water 11 days, 64% decomposition (light) 11 days, 58% decomposition (dark) Vehicle: CMC	(*119*)

Fluorodopan

The reactivity of the haloalkylamides such as fluorodopan (NSC-73754) depends on the rate of disassociation of the halogen ion. Because the fluorine ion in the fluorodopan molecule practically does not dissociate, it can be considered as a monofunctional alkylating agent (*120*).

An investigation of fluorodopan has shown that the general toxic effect on animals is decreased fiftyfold as compared with dopan, whereas the high and the broad antitumor activity spectrums are retained (*125*).

The advantages of fluorodopan over dopan include 1) rapid reversibility of the toxic effect on hematopoiesis, 2) milder disturbance of granulocytopoiesis, 3) absence of damage to the mucous membrane of the intestine, and 4) the long period of manifestation of the antitumor effect after a single administration of an MTD (*126*). The most appropriate manner of administration is in large doses with an interval of 5–7 days.

In a study of the mechanism of action of fluorodopan, the concentration that caused 50% suppression of DNA synthesis in ascites tumor cells after a brief incubation was five times higher than for dopan. The accumulation of labeled precursors in the form of nucleoside triphosphates is indicative of a block at the level of DNA and RNA polymerase (*127*).

Fluorodopan does not cause the appearance of cross-links in the DNA molecules of tumor cells, and the concentrations at which the apparance of breaks in DNA are observed are considerably higher than those of dopan. Thus the alkylating capacity of fluorodopan is greatly reduced in comparison with dopan, and this is reflected in the characteristic features of its biologic effects.

Sarcolysin

Sarcolysin (NSC-14210) is a drug of high selectivity and broad-spectrum antitumor activity. When administered to rats in a single MTD (12 mg/kg), it caused total resorption of a number of transplantable tumors with only a moderate toxic effect on the normal tissues. The side effects on the organism are manifested chiefly in a reversible suppression of hematopoiesis. Although the bone marrow regenerates rapidly, the lymphoid tissue does so more slowly (*120*). Larionov proposed that the high selectivity of the antitumor effect of sarcolysin is related to the fact that the natural carrier, phenylalanine, serves as a conductor of the cytotoxic group, predominantly into the tumor cell.

Indirect confirmation of this hypothesis is provided by data on the extensive biologic activity of the L isomer of sarcolysin (melphalan) as compared with the D isomer and the observation that the antitumor effect of sarcolysin can be weakened by simultaneous administration of massive doses of tyrosine (*128*). It is possible that the antimetabolite properties of sarcolysin are manifested at the membrane level in competition with a metabolite for cell entry. Also, sarcolysin, like other chlorethylamines, alkylates nucleic acids and proteins of tumors and normal tissues with the appearance of cross-links and breaks in DNA molecules and cross-links between the DNA and nuclear proteins. Alkylation of DNA and nuclear proteins results in the disturbance of the DNA replication processes, transcription, and mutagenic effects.

As opposed to nitrogen mustard and other chlorethylamines, sarcolysin in therapeutic doses disturbs the energy balance of tumor cells by acting on the mitochondria as an uncoupling agent (*129*).

Phenthyrine

Phenthyrine (NSC-275658) is highly effective not only against many transplantable sarcomas and melanomas of mice and rats but also against spontaneous tumors of dogs (e.g., transitional cell sarcoma, tumors of the ovary, thyroid, and breast).

The toxicity of phenthyrine depends on the route of administration. The LD50 is 30–60 mg/kg when administered iv to mice and rats and increases by an order of magnitude when given orally (*130*). At high doses, phenthyrine damages the lymphoid organs, the gastrointestinal tract, the liver, kidneys, thyroid glands, sex organs, and heart. In therapeutic doses, it may affect hematopoiesis, the gastrointestinal tract, and the heart.

One characteristic feature of the drug is its high immunodepressive action (*131*); another is its effect on the endocrine system. Phenthyrine causes a bloody discharge from the vagina of dogs, up to the point of uterine hemorrhaging, as well as lactation changes in the mammary gland and its tumors (*132*).

The toxic effect of phenthyrine on the thyroid gland can indirectly explain its high immunodepressive properties because of the relationship between the immunologic reactivity of the organism and the production of thyroxine. Also, the sensitivity of the thyroid gland to phenthyrine merits particular attention because the drug is a nitrogen mustard analog of thyroxine.

Palphicerin

Palphicerin (NSC-183734) displayed antitumor activity in experiments not only against tumors sensitive to chlorethylamines but also against nonsensitive tumors (*133*).

The drug was injected sc into dogs for 5 days in doses of 30 and 60 mg/kg and administered orally in single doses of 15 and 60 mg/kg. When parenterally administered, the toxicity was manifested in body weight loss, dyspepsia, a decline in the total number of leukocytes and lymphocytes, and impaired coordination of movement. The 60-mg/kg dose resulted in the death of the dogs. Smaller doses impaired muscular coordination, which was not restored in the course of several months.

A histologic study of the organ tissues showed changes in the cerebellum, with destruction of the granular layer of cells and interstitial cell edema. The introduction of palphicerin into the stomachs of dogs and mice does not cause the disturbed coordination of their movements shown by sc or ip administration in therapeutic doses. Thus the toxicity of the drug for brain tissue varies with its route of administration.

Phenestrol

The cytostatic hormone phenestrol (NSC-183736) combines the properties of an alkylating agent and an estrogen. This action is manifested not only in its effect on tumor growth but also on hematopoiesis. Like phenester, but to a lesser degree, phenestrol suppresses lymphopoiesis and stimulates granulocytopoiesis but more weakly than does sinestrol. Thus the alkylating and hormonal properties of the cytostatic hormone appear less pronounced than its individual components.

Hormonal properties of phenestrol are manifested in its effect on the target tissue. In rats, it causes an increase in the weight of the uterus, adrenals, and pituitary, and hyperplasia of the mammary glands to a lesser degree than sinestrol. The drug reduces the weight of the ovary, seminal vesicles, and the ventral lobe of the prostate gland (*134, 135*). Also, phenestrol possesses a prolonged estrogenic effect not found with sinestrol: It sharply increases the duration of estrus in gonadectomized mice and rats and inhibits for an extended period the production of follicle-stimulating pituitary hormone. Phenestrol significantly retards the growth of hormone-dependent tumors only in gonadectomized mice and rats (*135*).

Distron

The biologic characteristics of the cytostatic hormone distron (NSC-183735) are also related to the specific properties of its components. However, as opposed to phenestrol, distron has a much broader spectrum of action on transplantable, induced, and spontaneous tumors of animals that are relatively insensitive to alkylating agents and hormones (*136, 137*).

Although its properties are not cumulative, distron causes an extensive and prolonged lymphotoxic effect in dogs without lowering the total leukocyte count.

This cytostatic hormone manifests androgenic and anabolic properties and is similar to testosterone propionate in its androgenic activity but stronger in its anabolic effect. The drug displays nephrotoxicity, cardiotoxicity, and some neurotropism in dogs.

Judging by the nature of the effect on the process of transcription and metabolism of newly synthesized RNA in tumor cells and the spleen of mice, one can conclude that distron does not differ from phenester. Both drugs, when administered in a single maximum permissible dose, at first suppress transcription of pre-rRNA, and then the suppression is replaced by stimulation and accumulation in the nucleus and cytoplasm of unusual post-rRNA, which may be either incomplete transcripts or the products of disturbed processing. Distron is bound to the cytoplasmic receptors of androgens in normal tissues and tumors.

Prospidine

Whereas prospidine (NSC-166100) suppresses the growth of a large number of transplantable tumors of mice and rats up to the point of total regression of some of them, it is entirely inactive against transplantable leukemias.

Prospidine differs from the other antitumor compounds in its broad therapeutic scope and, consequently, its significant selectivity of action (*138, 139*).

A study of the pharmacokinetics of [^{14}C]prospidine revealed its rapid (within 2 hr) disappearance from the blood after iv administration; the greater part of the radioactive label is eliminated in the urine. The distribution of radioactivity in the tissues differs basically from that of other drugs. Prospidine accumulates in large quantities in the kidneys, lungs, upper respiratory tract, skin, intestine, pancreas, bones, and to a lesser degree in the spleen and lymph nodes. The slow elimination of the radioactive compound from the larynx, trachea, and major bronchi and from the cells of the hyaline cartilage of these organs is characteristic (*140*). Thus the character of the distribution of the drug partly explains its low toxicity and the absence of a suppressive effect on hematopoiesis.

As evidenced by the mechanism of action on the tumor cell, prospidine also differs from other alkylating compounds. It neither has an immunodepressive effect nor does it suppress the incorporation of [^{3}H]dThd into DNA of sarcoma 45 cells. As opposed to dipin and fotrin, prospidine reduces the ionic permeability of the plasma membrane of the tumor cells (*141*).

The effect of prospidine on intracellular processes is apparently mediated by parts of the plasma membrane receptor system responsible for ionic homeostasis of the cell. Its selective attack on tumor cells may result from structural differences at the cell surface (*139*).

Fotrin

Fotrin (NSC-216135) has higher antitumor activity against transplantable tumors and leukemias than thiophosphamide, dipin, and thiodipin. Characteristic features of fotrin are the lower toxicity and less pronounced cumulative properties than for the other drugs mentioned above. Fotrin suppresses lymphocyte and granulocyte production to an equal degree. The leukocyte count returns to normal in 10–13 days after the administration of the drug (*142*).

A study of the pharmacokinetics of [^{32}P]fotrin revealed maximum accumulation of radioactivity (15 min after iv injection) in the blood, intestine, liver, thymus, and a minimum in the femur, bone marrow, and muscles. An intermediate position is occupied by the pituitary, thyroid, pancreas, spleen, lungs, and kidneys. With time, the level of radioactivity increases in the spleen, thymus, and pituitary, and in the other tissues it declines to the minimum in 2–4 days.

As evidenced by the distribution pattern, fotrin displays a certain affinity for organs rich in lymphoid tissue. The elimination of labeled fotrin occurs through the kidneys and intestine, with about 70% of the drug eliminated in the urine during the first 24 hours and 0.4% in the feces; during the following days, more of the isotope is eliminated through the intestine (*142*).

Diiodobenzotepa

Diiodobenzotepa (NSC-167781) displays high antitumor activity against carcinomas and mesenchymomas (*143*) and is distinguished by its therapeutic scope and prolonged antitumor effect.

Although it preserves the basic character of the biologic effect of the ethyleneimines, diiodobenzotepa differs from them in its its low toxicity (LD50 for rats, 500 mg/kg) and reduced effect on hematopoiesis. The stimulating action exerted on the thyroid gland may be the cause of a host-mediated effect of the drug on tumor growth (*144*).

Diazan

Diazan (NSC-271276) has considerable antitumor activity and a broad spectrum of action. The drug is low in toxicity, but when applied several times daily, its toxicity increases sharply, which is indicative of its cumulative properties (*145*).

With the use of autoradiography, diazan was shown to suppress DNA synthesis and reduce the mitotic activity of leukemia L1210 cells, thus blocking for a prolonged period the transition of the cells from the G_1-phase into the S-phase and from the S-phase into the G_2-period and mitosis. Cell reproduction is then restored, but the intensity of the DNA synthesis remains lowered (*146*).

When given in therapeutic doses to mice with leukemia L1210, diazan caused marked suppression of transcription without influencing the processing of the high molecular weight precursors of mRNA and rRNA (*147*).

Methylnitrosourea

As one of the few antitumor agents that penetrates the blood–brain barrier MNU (NSC-23909) is effective against intracerebral forms of leukemia L1210, sarcoma 180, Ehrlich tumor, and transplantable glioma 101/12.

The drug, equally active when administered parenterally and orally, is most effective in single-administration "shock" doses. The side effects of MNU include suppression of hematopoiesis (*147–149*). This cycle-nonspecific agent exerts a cytotoxic effect not only on proliferating but also on quiescent cells cultivated in vitro. A characteristic feature of its effect on the kinetics of cell proliferation in vivo is the suppression of DNA synthesis, the prolongation of the S- and G_2-phases, and the temporary blocking of the cells in the late interphase (*150*).

Like other nitrosourea derivatives, MNU undergoes metabolic transformations in the organism and tumor under the influence of microsomal hydroxylases (*151*). The products of these transformations, the methylcarbonium ion and isocyanate, enter into alkylation and carbamoylation reactions with nucleic acids, proteins, and the components of the membranes of normal and tumor cells that lead to disturbances in DNA replication, transcription, and translation (*152, 153*).

When MNU is administered in single therapeutic doses to mice with leukemia L1210 or Ehrlich ascites tumor, profound inhibition of transcription not only of mRNA but also of rRNA and a disturbance of the normal processing of the rRNA take place (*154*).

Ftorafur

In a study of the mechanism of action of ftorafur (NSC-148958), Meyren and Belousova (*155*) found that the drug blocks thymidylate synthetase. However, the lack of correspondence between the limited capacity of the drug to suppress the biosynthesis of thymidylate in tumor cells in vitro and its considerable antitumor activity in vivo led to the hypothesis that ftorafur is a latent form of 5-FU. Further work on the metabolism and pharmacokinetics of [^{14}C]ftorafur confirmed this hypothesis. Under the influence of nonspecific oxidases of the liver microsomes, the pseudoglycoside bond in the ftorafur molecule is broken, accompanied by the liberation of 5-FU.

Ftorafur, as opposed to 5-FU, circulates in the blood for a long time, assuring prolonged contact of endogenous 5-FU with tumor cells. Also, when ftorafur is administered in vivo there is less likelihood of the occurrence of high concentrations of 5-FU that will be toxic for normal tissues, again assuring high antitumor activity of ftorafur in the presence of low toxicity (*156*).

In studies with patients with neuroectodermal tumors of the brain, ftorafur penetrated well through the blood–brain barrier and accumulated predominantly in the tumorous brain tissues. These data served as a basis for a study of the efficacy of ftorafur in the treatment of brain tumors (*157*). Ftorafur is equally effective parenterally and orally.

Tomizin

Tomizin (NSC-216134) differs in its mechanism of antitumor action from the well-known folic acid antagonists. It suppresses dihydrofolate reductase as well as the enzyme which inactivates aminopterin. As a result of this activity, tomizin can be effective against tumors resistant to other folic acid analogs (*158*).

In in vitro experiments, tomizin selectively inhibited the division of tumor cells. With approximately comparable activity to methotrexate in antitumor activity, tomizin has less acute or cumulative toxicity.

A study of the pharmacokinetics of [^{35}S]tomizin administered iv to rats with sarcoma M-1 and sarcoma 45 (*159*) revealed that it disappears from the blood rapidly (in 5–15 min). The highest level of radioactivity is recorded in the kidneys, adrenals, and pancreas, with lower levels in the lymph nodes, stomach, liver, small intestine, brain, and tumor. [^{35}S]Tomizin is eliminated from the body predominantly via the kidneys. The basic metabolic pathways are deamination and oxidation of the sulfur atom with the formation of 4-methoxypyrimido-6-thiazine and its sulfoxide. In addition, the N-5 nitrogen atom undergoes oxymethylation, and the amino group at C-6 undergoes acylation.

Carminomycin

Carminomycin (NSC-180024), an anthracycline anti-

biotic related in structure to daunorubicin and adriamycin, has a broad spectrum of antitumor action. The optimal mode for administration to animals is iv, with an interval of 96–120 hours between injections (*160*).

Judging by the mechanism of cytotoxic effect, carminomycin does not differ basically from daunorubicin. In a culture of *Micrococcus lysodeikticus,* carminomycin selectively suppresses DNA synthesis and, to a lesser degree, RNA synthesis. In ascites tumor cells, carminomycin inhibits DNA and RNA synthesis to an equal degree (*161*).

Like daunorubicin, carminomycin interacts in vitro with native DNA, RNA, polyribonucleotides, and purine nucleotides. The antibiotic stabilizes the double helical structure of DNA, and raises its melting point and viscosity. The result of the interaction of carminomycin with DNA is the suppression of the activity of RNA polymerase.

As opposed to many antitumor antimetabolites and antibiotics, carminomycin suppresses the repair synthesis of DNA (*161, 162*). Carminomycin differs from daunorubicin by its greater capacity to be absorbed from the gastrointestinal tract, a fact that is related to its pharmacokinetic characteristics and side effects (*163*).

Olivomycin

Olivomycin (NSC-76411), an antibiotic of the aurelic acid group, possesses a broad spectrum of antibacterial and antitumor action. At doses close to lethal, the antibiotic suppresses hematopoiesis and exerts a toxic effect on the kidneys of experimental animals. However, the acute toxicity of olivomycin is significantly lower than that of chromomycin, and its cumulative toxicity, also lower, characterizes it as a drug of higher selectivity of antitumor action (*164–167*). In its mechanism of cytotoxic effect, olivomycin resembles chromomycin and mithramycin. The antibiotics interact with native DNA in the Mg^{2+} or Mn^{2+} complex form and suppress its template activity during the process of transcription. Because the binding of olivomycin to DNA is strong, it leads to a prolonged retardation of the movement of the RNA polymerase along the DNA template and impairs the elongation of RNA. As opposed to dactinomycin, the process of intercalation does not play a major role in the interaction of this class of antibiotics with DNA (*168*).

Variamycin

Variamycin (NSC-269146) is active against a broad spectrum of tumors and leukemias in mice and rats. It differs from olivomycin and chromomycin, which are close to it in structure, in character of toxic effect and in other pharmacologic properties, but as indicated by the characteristics of its acute toxicity, variamycin is similar to mithramycin. After repeated therapeutic doses to rats, rabbits, and dogs, the toxic effect of variamycin was manifested by disturbances of liver and kidney functions and blood coagulation processes (*169*).

[^{14}C]Variamycin accumulates during the first hour after administration to rats in the blood, kidneys, liver, and spleen. No tendency for the radioactivity in the spleen to subside is noted in the course of 24 hours (*170*).

Variamycin penetrates the blood–brain barrier and accumulates predominantly in the intracranial tumor (multiform glioblastoma of rats), compared with normal brain tissue (*170*).

The mechanism of antitumor action of variamycin, like that of other antibiotics of this group, is based on its ability to form strong complexes with the DNA of the tumor cells and selective suppression of RNA synthesis (*171*). The parts of the DNA to which the variamycin and mithramycin are bound are common. They are rich in G–C pairs, which suggests the selective inhibition of the synthesis of ribosomal RNA by the antibiotic.

The products of partial degradation of variamycin, tetraozide and triozide weakly inhibit the synthesis of RNA in animal cells and in noncellular systems. The aglycone of variamycin is inactive as an inhibitor of RNA synthesis.

Variamycin exerts a strong immunodepressive effect at one-half the LD50 dose when given 24 hours before immunization. The administration of the antibiotic after antigenic stimulation does not reduce the immune response.

Reumycin

Reumycin (NSC-99733) belongs to the group of triazine antibiotics and is the dimethyl analog of fervenulin.

As an antitumor drug, it is effective against Ehrlich carcinoma, sarcoma 37, adenocarcinoma 755, and lympholeukemia L-5278Y, but it is inactive against leukemias L1210 and La. Reumycin is moderately toxic and has a high selectivity of antitumor action (*172*).

With prolonged iv administration at an MTD to dogs, reumycin caused leukopenia, thrombocytopenia, a change in the EKG, and a reduction in the clotting capacity of the blood. At toxic doses, it disturbed the functions of the kidneys and liver, exerted an immunodepressive effect, and increased the permeability of the vessel walls (*173*).

Like other triazine antibiotics, reumycin is an autooxidizable electron acceptor from flavin NADH-cytochome-b_5 oxidoreductase. The mechanism of antitumor action of reumycin is related to the effective oxidation of cytoplasmic NADH that leads to the disruption of energy metabolism and biosynthetic processes. In particular, reumycin suppresses RNA synthesis in tumor cells (*173*).

Chanerol

Chanerol (NSC-183737) is a drug of plant origin, characterized by unusual antitumor activity and low toxicity (*174, 175*). Judging by its characteristic features, chanerol is a lectin that differs from phytohemagglutinin by the absence of nitrogen in the molecule.

Compared with other lectins, chanerol has high antitumor activity, which correlates with its agglutinating capacity (*174, 175*).

A toxicity study of chanerol when given to animals (mice, rats, guinea pigs, rabbits, and dogs) showed that

a primary contributing factor to its toxic effect on the organism was the impairment of the coagulating and anticoagulating functions of the blood. These disturbances lead to thrombosis of the capillaries, disturbed microcirculation, and focal hemorrhaging. The intensity of the above-noted changes and their localization are determined not only by the magnitude of the dose of the drug used, but also by the anatomicophysiologic characteristics of the capillary channels of the internal organs (*176, 177*). An important characteristic of chanerol is the phenomenon of resistance of animals to repeated administration that may be used to prevent the development of the thrombohemorrhagic syndrome in animals.

The structures and solubility characteristics of a number of the Soviet drugs included in the joint study are presented in table 2.

TABLE 2.—*Drugs from the USSR included in the program of American–Soviet research*

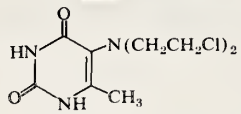
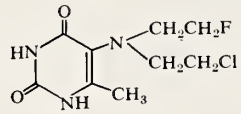
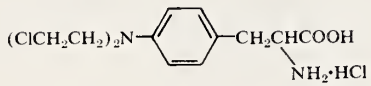
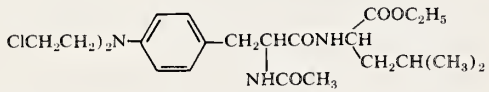
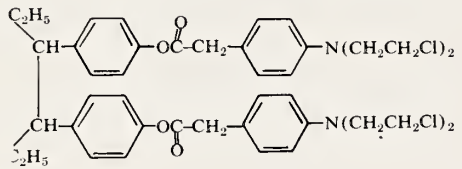
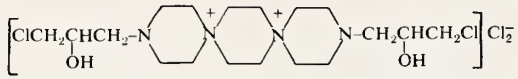
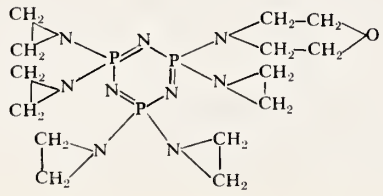
NSC No.	Compound name	Structural formula	Solubility	Institute conducting research	References
44629	Dopan		Poorly soluble in alcohol; practically insoluble in water	OSC, AMS, USSR	(*122*)
73754	Fluorodopan		Soluble in acetone, chloroform; practically insoluble in water	" " "	(*126*)
14210	Sarcolysin		Readily soluble in water but poorly soluble in ethyl alcohol	" " "	(*178*)
167780	Asaley		Soluble in alcohol, ethyl acetate, chloroform; insoluble in water	" " "	(*179*)
183736	Phenestrol		Poorly soluble in ethyl acetate; soluble when heated in DMSO (1.7%), benzyl alcohol (4%), benzyl benzoate (5.5%)	" " "	(*134*)
183735	Distron		Readily soluble in chloroform but poorly soluble in 95% ethanol; insoluble in water	" " "	(*180*)
183734	Palphicerin		Soluble in chloroform and ether but poorly soluble in alcohols; insoluble in water	" " "	(*180*)
166100	Prospidine		Readily soluble in water but poorly soluble in alcohol; practically insoluble in ether and chloroform	All-Union Scientific Research Chemical-Pharmaceutical Institute, MMP, USSR	(*181*)
216135	Fotrin		Readily soluble in water, 95% alcohol, chloroform, soluble in acetone, but only slightly in ether	All-Union Scientific Research Chemical-Pharmaceutical Institute, MMP, USSR	(*182*)

TABLE 2.—*Drugs from the USSR included in the program of American–Soviet research (continued)*

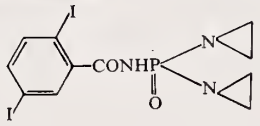
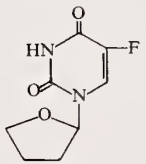
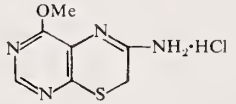
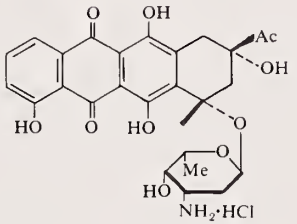
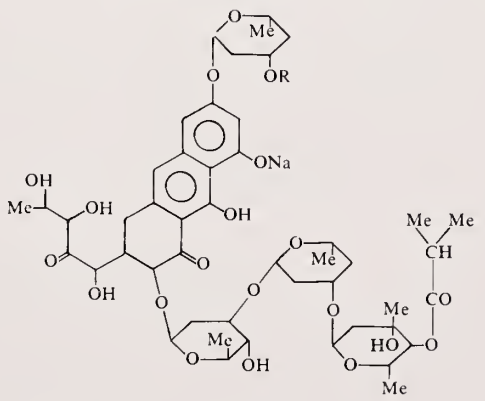
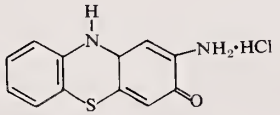
NSC No.	Compound name	Structural formula	Solubility	Institute conducting research	References
167781	Diiodobenzotepa		Poorly soluble in chloroform, 95% ethyl alcohol; insoluble in water	Kiev Research Institute for Pharmacology and Toxicology, Ministry of Health, Ukrainian SSR	(*183*)
148958	Ftorafur		Readily soluble in water, alcohol	IOS Academy of Sciences, Latvian SSR, and OSC, AMS, USSR	(*184*)
216134	Tomizin		Readily soluble in water, methanol	All-Union Scientific Research Chemical-Pharmaceutical Institute, MMP, USSR	(*185*)
180024	Carminomycin		Readily soluble in water, methanol	Institute for the Search for New Antibiotics, AMS, USSR	(*186*)
76411	Olivomycin		Readily soluble in water, alcohol	Institute for the Search for New Antibiotics, AMS, USSR	(*187*)
196869	Aton		Soluble in alcohol, aqueous alcohol, dioxan, DMFA	OSC, AMS, USSR	(*188*)
183737	Chanerol (polyphenol from tannin group)		Readily soluble in water, alcohol	" " "	(*175*)

TABLE 2.—*Drugs from the USSR included in the program of American–Soviet research (continued)*

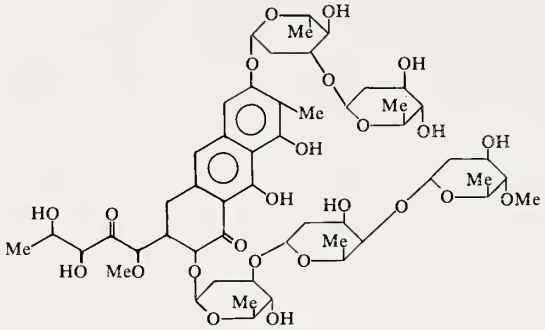
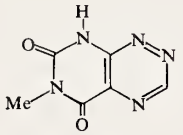
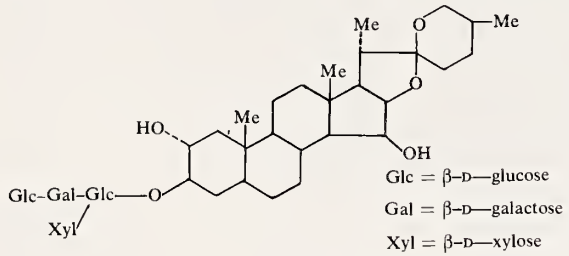
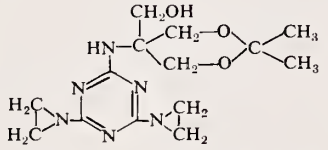
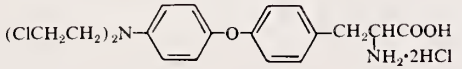
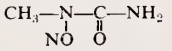
NSC No.	Compound name	Structural formula	Solubility	Institute conducting research	References
183738	Colchizin (synthetic derivative of colchicine)		Readily soluble in alcohol, moderately in water, 6% solution in 10% alcohol	" " "	(*189*)
271276	Diazan	$N_2CHCOCH_2CH_2COCHN_2$	Readily soluble in water, poorly soluble in hexane, octane	Institute for Chemical Physics, AS, USSR	(*145*)
269146	Variamycin		Readily soluble in lower alcohols, moderately in water	All-Union Research Institute for Antibiotics, Ministry of Health, USSR	(*190*)
99733	Reumycin		Soluble in water	All-Union Research Institute for Antibiotics, Ministry of Health, USSR	(*191*)
275653	Agavoside (steroid glycoside)		Soluble in water	OSC, AMS, USSR	(*192*)
23471	Digitonin		Soluble in water, DMSO	" " "	(*192*)
275654	Funkioside (steroid glycoside)		Insoluble in water	" " "	(*192*)
275655	Vitalboside (triterpene glycoside)		Insoluble in water	" " "	(*193*)

TABLE 2.—*Drugs from the USSR included in the program of American–Soviet research (continued)*

NSC No.	Compound name	Structural formula	Solubility	Institute conducting research	References
275652	Glucomannan (polysaccharide from roots of *Eremurus comosus*)		Soluble in water to 8%, DMSO, insoluble in alcohol	OSC, AMS, USSR	(*194*)
275656	Dioxadet		Soluble in water, readily soluble in methyl alcohol, poorly soluble in vegetable oils	N. N. Petrov Research Institute for Oncology, USSR	(*195*)
275658	Phenthyrine		Soluble in water and alcohol	OSC, AMS, USSR	(*130*)
23909	Methylnitrosourea		Moderately soluble in water (up to 1%), well in organic solvents (acetone, DMFA, DMSO), soluble in lipids	Institute for Chemical and Physics, Academy of Science, USSR	(*196*)

Chapter II: Methods of Selecting Antitumor Drugs in the United States and Soviet Union [1]

In this chapter, information is presented on the methodologic techniques used in the United States and the USSR in screening for new antitumor drugs.

A: TEST SYSTEMS USED IN THE UNITED STATES

Lymphoid Leukemia L1210

Origin

This tumor line originated as a lymphocytic leukemia in a DBA/2 female mouse in 1948 after the skin was treated with 0.2% 20-MCA in ethyl ether (*197*).

Source [2]

General

Routinely, when the L1210 system is used as a primary drug screen, ascitic fluid from stock tumor-bearing DBA/2 mice is implanted ip into (C57BL/6 × DBA/2) BDF_1 or (BALB/c × DBA/2) CDF_1 mice. Treatment is begun on the following day. Drug effectiveness is assessed on the basis of survival time of the mice. Results are expressed as a percentage of the control survival time.

Abbreviations: ic = intracerebral(ly); MST = median survival time; NCI = National Cancer Institute; ILS = increased life-span; 3- or 20-MCA = 3- or 20-methylcholanthrene; LL = Lewis lung (tumor); OSC AMS = Oncological Scientific Center, Academy of Medical Sciences (USSR); LD50 = median lethal dose; OD = optical density; ED50 = median inhibitory concentration.

[1] This chapter was prepared by I. Kline and G. N. Platonova.

[2] Tumor line was obtained from frozen tumor bank maintained at Arthur D. Little, Inc., Cambridge, Massachusetts.

[3] Range is 3 g, with a minimum weight of 18 g for males and 17 g for females.

[4] Animal selection is based on weight; normally, the mice are 6–8 wk old.

[5] A single sex is used for all test (treatment) and control mice in 1 experiment.

[6] A test group is defined as 1 experimental group receiving one dosage level of drug.

[7] Number depends on No. of test groups (G) and No. of mice in each test group (M); No. of control animals = $\sqrt{G} \times M$. Example: If an experiment contains 25 test groups of 6 mice each, the No. of control mice is $\sqrt{25} \times 6 = 30$.

[8] T/C% = test group mean survival time/control group mean survival time × 100. The percentage increase in life-span over control (ILS%) is computed as follows: ILS% = T/C% − 100.

Propagation of stock tumor

Animals: DBA/2

Inoculum: Consisted of 0.1 ml of diluted (sterile physiologic saline) ascitic fluid containing 10^5 cells (ip), 10^6 cells (sc), or 10^7 cells (iv); 0.5 ml diluted blood containing 2×10^5 cells drawn from a leukemic mouse (ic).

Implant site: ip, sc, or ic on day 0.

Time of transfer for propagation or for drug testing: Day 6 or 7.

Drug testing

Animals: BDF_1 or CDF_1 mice

Weight range: [3]

Age range: [4]

Sex: [5]

No. of mice/test group: [6] 3–10, usually 6

No. of control mice/experiment: [6, 7] 3–10, usually 6

Testing schedule: Daily, ip, days 1–9; once on days 1, 5, and 9; or once on day 1 only depending on the amount of available material

Dosage: For initial testing, three serial diluted dosage levels (D, D/2, and D/4) are used.

Evaluation

Acceptable control mean survival time: 8–11 days

Parameter of effect: [8]

Minimum criterion for activity: T/C ≥ 125%

Day of final evaluation (day on which survivors are discarded): Day 30 or 45.

Lymphocytic Leukemia P388

Origin

This tumor line originated as a lymphocytic leukemia in 1955 in a DBA/2 female mouse after the skin was painted with 3-MCA (*198*).

Source [2]

Geueral

Routinely, when the P388 system is used as a primary screen, ascitic fluid from stock tumor-bearing DBA/2 mice is implanted ip into BDF_1 or CDF_1 mice. Treatment is begun on the following day. Drug effectiveness is assessed on the basis of survival time of the mice. Results are expressed as a percentage of the control survival time.

Propagation of stock tumor

Animals: DBA/2 mice
Inoculum: Consisted of 0.1 ml of diluted (sterile physiologic saline) ascitic fluid containing 10^6 cells ip, 10^7 cells sc or iv, or 0.05 ml of diluted blood containing 3 X 10^5 cells drawn from a leukemic mouse (ic)
Implant site: ip, sc, or ic on day 0
Time of transfer for propagation: Day 7
Time of transfer for drug testing: Day 6 or 7

Drug testing

Animals: BDF_1 or CDF_1
Weight range: [3]
Age range: [4]
Sex: [5]
No. of mice/test group: [6] 6
No. of control mice/experiment: [7]
Testing schedule: Usually ip daily from days 1 to 9
Dosage: For initial testing, three serial diluted dosage levels (D, D/2, and D/4) are used.

Evaluation

Acceptable control mean survival time: 9–14 days
Parameter of effect: [8]
Minimum criterion for activity: T/C = 125%
Day of final evaluation: Day 30 or 45

B16 Melanoma

Origin

This tumor line arose spontaneously in 1954 on the skin at the base of the ear in a C57BL/6 mouse (*199, 200*).

Source

The B16 tumor was supplied by The Jackson Memorial Laboratory in 1967 as a subcutaneous tumor in C57BL/6 mice. Lines used in this program were generated in vivo from the frozen tumor bank.[2]

General

For drug testing, a homogenate of subcutaneously grown tumor from C57BL/6 mice is implanted either ip or sc into BDF_1 mice. When the tumor is implanted ip, it grows as multiple discrete masses lining the peritoneal cavity and not as ascites tumor. The subcutaneous B16 is considerably more resistant than the intraperitoneal to drug therapy. In general, ip treatment is begun on the day after either ip or sc tumor implantation. Drug effectiveness is usually assessed on the basis of the survival time of the mice. Results are normally expressed as a percentage of the control survival time.

Propagation of stock tumor

Animals: C57BL/6 mice
Inoculum: Tumor fragment (approximately 25 mg) is implanted by trocar or 12-gauge needle. Alternatively, 0.5 ml of a tumor homogenate (1 g tumor in 10 ml physiologic saline) may be implanted sc, or 0.05 ml inoculated ic.
Implant site: sc or ic on day 0
Time of transfer for propagation: Day 10–14
Time of transfer for drug testing: Day 10–14

Drug testing

Implant site: Tumor homogenate implanted ip or sc
Animals: BDF_1
Weight range: [3]
Age range: [4]
Sex: [5]
No. of mice/test group: [6] 10
No. of controls/experiment: [7]
Testing schedule: In general, ip treatment is given daily from days 1 through 9. However, the treatment schedule may be varied for an individual drug based on results obtained in other test systems.
Dosage: Dose–response testing is used. The actual dosage levels and No. of dosage levels are determined by existing data from other test systems.

Evaluation

Acceptable control median survival time: For ip implanted B16, MST is 14–22 days.
Parameter of effect: [8]
Day of final evaluation: Day 90

Friend Virus Leukemia (Solid)

Origin

A pathogenic virus causing a leukemia-like disease in mice was isolated by Dr. C. Friend from mouse donors which had received inoculations of cell-free extracts prepared from a transplanted mouse carcinoma (*201*).

Source [2]

General

Tumor fragments are transplanted sc into BDF_1, DBA/2, or Swiss mice. Treatment (ip) is begun on the following day and continued to day 11. Drug efficacy is assessed on the basis of tumor weight inhibition, which is determined on day 12.

Propagation of stock tumor

Animals: BDF_1, DBA/2, Swiss mice
Inoculum: Fragments
Implant site: sc
Time of transfer for propagation or drug testing: Days 13–14

Drug testing

Animals: BDF_1, DBA/2, Swiss mice
Weight range: [3]
Age range: [4]
Sex: [5]
No. of mice/test group: [6] 8–10
No. of control mice/experiment: [7]

Evaluation

Parameter of effect: [9] Tumor weights on day 12

Lewis Lung Carcinoma

Origin

This tumor arose spontaneously as a carcinoma of the lung in a C57BL/6 mouse in 1951 in the laboratory of M. R. Lewis [Lewis MR: Unpublished data; (*202, 203*)].

Source

The Lewis lung carcinoma was obtained in 1961 from the Sloan-Kettering Institute, which had received it in 1954 from M. R. Lewis.[2]

General

The system has the extension of survival time as the principal parameter of response. The subcutaneously grown tumor from C57BL/6 stock tumor mice is implanted sc as a 2- to 4-mm fragment or im as a 2×10^6 cellular homogenate into BDF_1 mice. Initial testing involves early treatment usually beginning on day 1. Tumor weight inhibition (extrapolated from tumor size) may be used as an ancillary parameter.

Propagation of stock tumor

Animals: C57BL/6 mice
Inoculum and implant site: Tumor fragment (2- to 4-mm or 25 mg) implanted sc by trocar into the axillary region.
Time of transfer for propagation: Day 12–14
Time of transfer for drug testing: Day 12–14

Drug testing

Implant site: Tumor fragments (*see* above) are implanted sc. Alternatively, a homogenate (2×10^6 cells) implanted im into the right hind leg, or tumor homogenate (1×10^5 cells) may also be implanted iv.
Animals: BDF_1
Weight range: [3]
Age range: [4]
Sex: [5]
No. of mice/test group: [6] 10
No. of control mice/experiment: [7]
Testing schedule: Treatment (ip) is given daily from days 1 through 9 or 11. However, the treatment schedule and day of initiation of treatment may vary for a specific drug under study.
Dosage: Dose–response testing is used. Dosage levels are determined from existing data derived from other test tumor systems.

Evaluation

Acceptable control median survival time: 18–28 days
Parameter of effect: [8]
Minimum criterion for activity: T/C = 150%
Day of final evaluation: Day 90

AKR Lymphocytic Leukemia (Transplantable, L-AKR)

Origin

Spontaneous virus leukemia arises in approximately 70% of the AKR mice when they reach 1 year of age (*201*).

Source

AKR mice were procured from Mammalian Genetics and Animal Production Section, Division of Cancer Treatment, NCI.

General

When enlarged spleens are distinctly palpable ($\geq$ 600 mg), they are transplanted ip into AKR mice. Treatment generally is begun on the following day. Drug effectiveness is assessed on the basis of the survival time of the mice.

Progagation of stock tumor

Animals: AKR mice
Inoculum: Spleens weighing $\geq$ 600 mg are used for donor tissues. The inoculum, prepared at a concentration of 1:10, is administered ip.
Time of transfer for propagation or for drug testing: When spleens are distinctly palpable ($\geq$ 600 mg), they are transplanted.

Drug testing

Animals: AKR mice
Weight range: [3]
Age range: [4]
Sex: [5]
No. of mice/test group: [6] Usually 8–10
No. of control mice/experiment: [7]
Testing schedule: Generally daily, days 1–9

Evaluation

Parameter of effect: [8]

[9] Tumor inhibition percent = control tumor wt − treated tumor wt/control tumor wt × 100.

Lymphatic Leukemia P1534

Origin

This tumor line arose spontaneously in the thymus of a DBA/2 mouse in 1940 (*204*).

Source [2]

General

A splenic brei from mice with advanced leukemia is inoculated ip into DBA/2 or CDF_1 mice. Treatment is started on the following day. Drug efficacy is assessed on the basis of the survival time of the mice.

Propagation of stock tumor

Animals: DBA/2
Inoculum: Spleen brei at a concentration of 1:100. Spleens are removed from mice with advanced leukemia (day of transfer, 10) and are implanted ip.

Drug testing

Animals: DBA/2 or CDF_1
Weight range: [3]
Age range: [4]
Sex: [5]
No. of mice/test group: [6] Usually 6
No. of control mice/experiment: [7]
Testing schedule: Daily, days 1–9, or as indicated; treatment ip

Evaluation

Parameter of effect: [8]
Day of final evaluation: Day 30

Ehrlich Ascites Tumor

Origin

This is an undifferentiated tumor that originated spontaneously as a carcinoma. Paul Ehrlich reported in 1907 on several transplantable tumors of the mouse. The various Ehrlich tumors carried in transplantation today as the Ehrlich ascites tumors were derived undoubtedly from one of the original lines of Ehrlich's carcinomata (*205*).

Source [2]

General

Ascitic fluid from stock Swiss mice is implanted ip into recipient Swiss mice. Treatment is started on the following day. Drug effectiveness is assesed on the basis of inhibition of ascites volume (or weight).

Propagation of stock tumor

Animals: Swiss mice
Inoculum: 10^6 cells implanted ip
Time of transfer for propagation or drug testing: Day 7

Drug testing

Animals: Swiss mice
Weight range: [3]
Age range: [4]
Sex: [5]
No. of mice/test group: [6] Usually 6
No. of control mice/experiment: [7]
Testing schedule: Usually daily, days 1–7, ip

Evaluation

Parameter of effect: Day 12: percent tumor ascites inhibition = (control − treated)/control × 100.

Gardner 6C3HED Lymphosarcoma

Origin

This lymphosarcoma was induced with estradiol benzoate in the thymus gland of a C3H mouse in 1941 (*204*).

Source [2]

General

Ascitic fluid from stock C3H mice is implanted ip into C3H or (C3H × AKR) $CHKRF_1$ mice. Treatment is begun on the following day. Drug efficacy is assessed on the basis of the survival time of the mice.

Propagation of stock tumor

Animals: C3H mice
Inoculum: Ascitic fluid containing 10^6 cells is implanted ip.
Time of transfer for propagation or drug testing: Day 7

Drug testing

Animals: C3H or $CHKRF_1$ mice
Weight range: [3]
Age range: [4]
Sex: [5]
No. of mice/test group: Usually 6
No. of control mice/experiment: [7]
Testing schedule: Daily, days 1–9, ip

Evaluation

Parameter of effect: [8]
Day of final evaluation: Day 30

Mecca Lymphosarcoma

Origin

This lymphosarcoma arose spontaneously in the region of a mammary gland from a transplanted carcinoma in an AKR/M mouse in 1949 (*204*).

Source [2]

General

Ascitic fluid from stock AKR/N mice is transplanted ip into $CHKRF_1$ mice. Treatment is begun the next day. Drug effectiveness is assessed on the basis of survival time.

Propagation of stock tumor

Animals: AKR/N mice
Inoculum: Ascitic fluid containing 1×10^6 cells is implanted ip.
Time of transfer for propagation or drug testing: Day 7

Drug testing

Animals: $CHKRF_1$ mice
Weight range: [3]
Age range: [4]
Sex: [5]
No. of mice/test group: 6–10, usually 6
No. of control mice/experiment: [7]
Testing schedule: Daily, days 1–9, treatment ip

Evaluation [8]

Day of final evaluation: Day 30

P-815 Mast Cell Leukemia (Ascites)

Origin

This leukemia originated in a DBAf/2 mouse painted repeatedly with 3-MCA (*206*).

Source [2]

General

Ascitic fluid from stock tumor-bearing CDF_1 mice is implanted ip into BDF_1 or CDF_1 animals. Treatment is started the next day. Drug efficacy is assessed on the basis of the survival time of the mice.

Propagation of stock tumor

Animals: CDF_1
Inoculum: Ascitic fluid diluted to a concentration of 1×10^6 cells is implanted ip.
Time of transfer for propagation or drug testing: Day 7

Drug testing

Animals: BDF_1 or CDF_1 mice
Weight range: [3]
Age range: [4]
Sex: [5]
No. of mice/test group: 6–10, usually 6
No. of control mice/experiment: [7]
Testing schedule: Daily, days 1–9 or 15, treatment ip

Evaluation

Parameter of effect: [8]
Day of final evaluation: Day 30

LPC-1 Plasma Cell Neoplasm

Origin

This neoplasm originated in a male BALB/c mouse that had received ip injections of mixtures of incomplete Freund's adjuvants and heat-killed staphylococci in 1960 (*207*).

Source [2]

General

Ascitic fluid from stock tumor-bearing BALB/c mice is inoculated ip into recipient BALB/c mice. Treatment is initiated between days 14 and 19 and continued for 28 days. Drug effectiveness is assessed on the basis of the survival time of the mice.

Propagation of stock tumor

Animals: BALB/c
Inoculum: Ascitic fluid containing 1×10^5 cells is inoculated ip.
Time of transfer for propagation or drug testing: Day 14–15

Drug testing

Weight range of mice: [3]
Sex: [5]
No. of mice/test group: 8–10, usually 8
No. of control mice/experiment: [7]
Testing schedule: Treatment (ip) is started between days 14 and 19 and continued for 28 days.

Evaluation

Parameter of effect: [8]

L-5178Y Lymphocytic Leukemia

Origin

A medium was developed that permitted the growth of an ascitic line of L-5178Y in tissue culture. This line produced a typical leukemia when inoculated into susceptible strains of mice (*208*).

Source [2]

General

Ascitic fluid from stock tumor-bearing DBA/2 mice is inoculated ip into BDF_1 mice. Treatment is started the following day. Drug is assessed on the basis of the survival time of the mice.

Propagation of stock tumor

Animals: DBA/2
Inoculum: Diluted ascitic fluid (0.1 ml) containing 1×10^6 cells (ip) or 1×10^7 cells (iv)
Implant site: ip or iv
Time of transfer for propagation or drug testing: Day 7

Drug testing

Animals: BDF_1
Weight range: [3]
Sex: [5]
No. of mice/test group: 6–10, usually 6
No. of control mice/experiment: [7]
Testing schedule: Daily, days 1–9 or 10; treatment ip

Evaluation

Parameter of effect: [8]
Day of final evaluation: Day 30

P-329 Reticulum Cell Sarcoma

Origin

This neoplasm arose in a female DBA/2 mouse after 5 skin paintings with 0.2% solution of 3-MCA in ether during the first 2 weeks of life (*209*).

Source [2]

General

The stock tumor is maintained in CDF_1 mice. Ascitic fluid at a concentration of 1×10^6 cells is implanted into CDF_1 or BDF_1 mice. Testing is generally started on day 1. Extension of survival time is the parameter of response used.

Propagation of stock tumor

Animals: CDF_1 mice
Inoculum and implant site: Ascitic fluid diluted to 1×10^6 is implanted ip.
Time of transfer for propagation or drug testing: Day 8

Drug testing

Implant site: Ascitic fluid is implanted ip
Animals: CDF_1 or BDF_1 mice
Weight range: [3]
Sex: [5]
No. of mice/test group: 6–8
No. of control mice/experiment: [7]
Testing schedule. Generally, ip treatment is given daily from days 1 to 9 or 10.

Evaluation

Parameter of effect: [8]
Day of final evaluation: Day 30

Reticulum Cell Sarcoma (Kelly; Mouse)

Origin

This sarcoma was induced in a newborn C57BL/6JN mouse with a single injection of 3-MCA (*210*).

Source [2]

General

A splenic suspension is prepared from tissue taken from a donor CDF_1 mouse and implanted ip into CDF_1 mice. Treatment is begun on day 1 or 5. Survival time is used to assess drug effectiveness.

Propagation of stock tumor

Animals: CDF_1 mice
Inoculum: Spleen taken from mice with advanced disease is diluted 1:6 and implanted ip.

Drug testing

Animals: CDF_1 mice
Weight range: [3]
Sex: [5]
No. of mice/test group: 8–10, usually 8
No. of control mice/experiment: [7]
Testing schedule: Treatment ip daily, days 5–15

Evaluation [8]

Day of final evaluation: Day 40

Carcinoma 1025

Origin

This carcinoma was induced in 1945 in the skin of AKR mouse with 20-MCA (*204*).

Source [2]

General

Tumor fragments are implanted sc in AKR or $CHKRF_1$ mice. Treatment is begun on the following day. Survival time is the basis for drug effectiveness.

Propagation of stock tumor

Animals: AKR or $CHKRF_1$ mice
Inoculum: Tumor fragments
Implantation site: sc
Time of transfer for propagation or drug testing: Days 12–14

Drug testing

Animals: $CHKRF_1$ or AKR mice
Weight range: [3]
Sex: [5]
No. of mice/test group: 8–10, usually 8

No. of control mice/experiment: [7]
Testing schedule: Treatment ip, days 1–5

Evaluation [9]

Weight is recorded on day 15.

Lymphocytic Leukemia P-288

Origin

This neoplasm originated in a DBA/2 male mouse after 20 skin paintings (three times weekly) with 0.2% 3-MCA in ether (*211*).

Source [2]

General

Ascitic fluid from donor DBA/2 mice is implanted ip into BDF_1 mice. Treatment is generally begun on the next day. Drug effectiveness is assessed on the basis of survival time of the mice.

Propagation of stock tumor

Animals: DBA/2
Inoculum: Ascitic fluid containing 10^6 cells is inoculated sc
Time of transfer for propagation or drug testing: Days 5–7

Drug testing

Animals: BDF_1 mice
Weight range: [3]
Sex: [5]
No. of mice/test group: 6–8, usually 6
No. of control mice/experiment: [7]
Testing schedule: Daily, days 1–10

Evaluation

Parameter of effect: [8]
Day of final evaluation: Day 30

Leukemia P-335

Origin

This tumor was induced in a DBA/2 mouse with 3-MCA (Potter M: Personal communication).

Source [2]

General

Ascitic fluid from stock CDF_1 mice is implanted ip into BDF_1 mice. Treatment is started on the following day. Drug effectiveness is assessed on the basis of survival time of the mice.

Propagation of stock tumor

Animals: CDF_1
Inoculum: Ascitic fluid containing 10^6 cells
Implant site: ip
Time of transfer for propagation or for drug testing: Day 7

Drug testing

Animals: BDF_1 mice
Weight range: [3]
Sex: [5]
No. of mice/test group: 6–8, usually 6
No. of control mice/experiment: [7]
Testing schedule: Daily, days 1–9; ip treatment

Evaluation

Parameter of effect: [8]
Day of final evaluation: Day 30

Lymphosarcoma P-1798

Origin

This lymphosarcoma arose in a BALB/c mouse that had received a 20% diethylstilbestrol–cholesterol pellet sc (*212*).

Source [2]

General

Tumor fragments or suspensions from donor BALB/c mice are implanted sc into BALB/c, CDF_1, or CAF_1 mice. Drug treatment is started the following day. Survival time or tumor weight is the basis for drug effect.

Propagation of stock tumor

Animals: BALB/c or CAF_1
Inoculum: Fragments or tumor brei at a concentration of 3 or 5×10^6 cells
Implant site: sc
Time of transfer for propagation or for drug testing: Days 12–14

Drug testing

Animals: BALB/c, CDF_1, or CAF_1
Weight range: [3]
Sex: [5]
No. of mice/test group: 8–10, usually 8
No. of control mice/experiment: [7]
Testing schedule: Daily, days 1–11

Evaluation

Parameter of effect: [8]
Alternative parameter: Tumor weight, day 12

Granulocytic Leukemia P-1081

Origin

This tumor was X-ray-induced in a DBA/2 mouse and was converted to the ascites form (Potter M: Personal communication).

Source [2]

General

Ascitic fluid from donor tumor-bearing BDF_1 mice is implanted ip into the same strain. Treatment is started the next day. Drug efficacy is assessed on the basis of ILS.

Propagation of stock tumor

Animals: BDF_1 mice
Inoculum: Ascitic fluid containing 1×10^6 cells
Implanted site: ip
Time of transfer for propagation or drug testing: Day 7

Drug testing

Animals: BDF_1 mice
Weight range: [3]
Sex: [5]
No. of mice/group: 6–8, usually 6
No. of control mice/experiment: [7]
Testing schedule: Daily, days 1–10; ip treatment

Evaluation

Parameter of effect: [8]
Day of final evaluation: Day 30

Melanotic (Cloudman) Melanoma S-91

Origin

This tumor arose spontaneously in 1937 at the base of the tail of a female DBA/2 mouse, an observation made by Dr. Cloudman at The Jackson Memorial Laboratory (*205*).

Source [2]

General

Fragments of tumor brei from stock tumor-bearing DBA/2 are implanted sc into BDF_1 mice. Treatment is begun the following day. Drug efficacy is assessed on the basis of inhibition of tumor weight.

Propagation of stock tumor

Animals: DBA/2
Inoculum: Fragments or tumor brei diluted 1:2
Implant site: sc
Time of transfer for propagation or drug testing: Day 21

Drug testing

Animals: BDF_1
Weight range: [3]
Sex: [5]
No. of mice/test group: 10
No. of control mice/experiment: [7]
Testing schedule: Daily, days 1–11; ip treatment

Evaluation

Parameter of effect: [9]
Day of evaluation: Day 21

Hepatoma 129

Origin

This tumor line was developed by the oral administration of carbon tetrachloride (0.2 cc of a 3% solution at weekly intervals in a male C3H mouse (*213*).

Source [2]

General

Fragments from tumor-bearing C3H mice are implanted sc into recipient C3H animals. Drug effectiveness is determined by inhibition of tumor weight.

Propagation of stock tumor

Animals: C3H mice
Propagation of stock tumor: Tumor fragments

Drug testing

Animals: C3H mice, tumor fragments for testing
Weight range: [3]
Sex: [5]
No. of mice/test group: 10
No. of control mice/experiment: [7]
Testing schedule: Days 5–14, sc treatment

Evaluation

Parameter of effect: [9] Day of tumor weight: day 15

Ependymoblastoma

Origin

The original tumor was induced by 3-MCA implantation in the brain of a mouse (*214*).

Source [2]

The experimental tumor used in these studies was the mutant strain derived by Ausman et al. (*215*).

General

The tumor is routinely propagated in C57BL/6 mice

by sc implantation of 2 × 2 × 8-mm fragments. The ic implantation was performed according to the technique described by Ausman and co-workers (*215*). In this technique, tumor fragments are expressed into the right cerebral hemisphere with a modified 19-gauge, 3-inch spinal needle. Treatments were generally given daily on days 1–5 unless noted otherwise. Drug effectiveness was assessed on the basis of survival time of the mice. Treatment results are expressed as a percentage of the control survival time.

Propagation of stock tumor

Animals: C57BL/6
Inoculum: Implantation of 2 × 2 × 8-mm fragments sc
Site: For drug testing, ic
Time of transplantation for propagation and drug testing: Days 12–14

Drug testing

Animals: C57BL/6 males
Weight range: 20–24 g
Age: Approximately 6 weeks old
No. of mice/test group: 6 mice/dose level
No. of control mice: Usually 1 group of 30 untreated control mice was inoculated with 25 drug-treated groups (6 mice each).
Testing schedule: Usually ip once daily on days 1–5

Evaluation

Acceptable control mean survival time: 17–21 days
Parameter of effect: [8]
Minimum criterion for activity: T/C ≧ 125%

Sarcoma 180

Origin

The primary tumor was found in the right axillary region of a white male mouse at necropsy, October 1914, in the laboratory of W. H. Woglam (Crocker Institute, New York, N.Y.). The tumor was diagnosed as a carcinoma. After transplantation, the tumor resembled a sarcoma (*205*).

Source [2]

General

Tumor fragments are implanted sc into Swiss mice. Treatment is begun the following day and continued daily until day 7. Drug effectiveness is based on tumor weight or survival time. The tumors are excised and weighed on day 9. Survival time results are expressed as a percentage of the control survival time.

Propagation of stock tumor

Animals: Tumor is not strain specific. Non-inbred Swiss albino mice are used.
Inoculum: Fragments
Site: sc
Time of transfer for propagation or drug testing: Day 6 or 7

Drug testing

Animals: Swiss mice
Weight range: [3]
Age range [4]
Sex: [5]
No. of mice/test group: 6–10, usually 8
No. of control mice/experiment: [7]
Testing schedule: Generally daily, days 1–7

Evaluation

Tunmor weight: Percent T/C = average test tumor wt/average control tumor wt × 100.
Survival time: [8]

Mammary Adenocarcinoma C3H/He

Origin

The virus-induced spontaneous mouse mammary adenocarcinoma has many common features with human breast cancer, e.g., anatomic morphology and invasiveness, growth and progression through a precancerous stage, genetic and hormone factors, and the general correlation of response of human and murine tumors to chemical agents (*216, 217*).

Source

Retired female C3H/He (C3H) breeders bearing spontaneous mammary adenocarcinomas were supplied by the Mammalian Genetics and Animal Production Section, NCI, after detection of the tumors in the course of routine handling.

General

Spontaneous tumors were dissected, cut into fragments, and implanted into the axillary region of the mice. Treatment usually was started when the tumors measured 6 mm in diameter. Treatment schedules of test agents depended on previous schedules of effectiveness in other tumor systems. Dose–response studies were used. Drug effectiveness was based on inhibition of local tumor growth and ILS compared with untreated control animals.

Propagation of stock tumor

Animals: C3H/He mice
Inoculum: Tumor fragments approximately 1 mm in diameter were implanted sc in the axillary region.
Time of transfer for propagation or drug testing: Shortly after palpable mammary tumors were detected

Drug testing

Animals: Retired female C3H/He (C3H) breeders (donors). Recipients were C3H/He for first generation tumor transplants.
Weight range: 18–26 g
Sex: Female
No. of mice/test group: Usually 9 mice/test group; control untreated groups contained 16 or more mice.
Testing schedule: Either ip or sc treatment generally was initiated when tumor measured approximately 4–6 mm. Treatment schedules were selected from previously demonstrated effective schedules in other tumor systems.

Evaluation

Inhibition of tumor growth: Tumor diameters were measured with vernier calipers. Tumor volumes were calculated with the formula of a prolate sphere $4/3\ \pi\ ab^2$, where a and b are the major and minor semiaxes (*218*).
Percent T/C = tumor volume of test group/tumor volume of control group × 100.
Increase in survival time:
Percent T/C = test group MST/control group MST × 100.

Adenocarcinoma Ca-755

Origin

This adenocarcinoma arose spontaneously in the mammary gland of a C57BL mouse in 1936 (*204*).

Source [2]

General

Tumor brei or fragments are implanted sc into BDF_1 mice. Treatment (ip) is started on the next day and generally is continued until day 11. Drug efficacy is assessed by tumor weight inhibition on day 12 or by survival time of the mice. Results are expressed as a percentage of the untreated control animals.

Propagation of stock tumor

Animals: C57BL/6 mice
Inoculum: 2 × 2 × 2-mm fragments are implanted sc via trocar or 1:10 tumor brei inoculated sc.
Time of transfer for propagation or drug testing: Days 10–14

Drug testing

Animals: BDF_1 mice
Weight range: [3]
Sex: [5]
No. of mice/test group: 8–10, usually 8
No. of control mice/experiment: [7]
Testing schedule: Daily, days 1–11 (generally ip)

Evaluation

Survival time: [8]
Tumor weight: [9]

In Vitro KB Cell Culture Screen

Origin

This tumor line was derived in 1954 from a human epidermoid carcinoma of the nasopharynx (*219*).

Source [2]

General

KB cells are cultivated in Eagle's Basal Medium plus 10% serum. Stock cells are fed 24 hours before testing. Test materials were added on days 0 or 1. Results are expressed as the dose that inhibits growth to 50% of control growth by 3 days after drug addition.

Drug testing

General: Three to five dose levels per material; two tubes per dose level.
Control group: Number varies according to number of test groups (n), according to the formula: $2\sqrt{n}$. Base-line protein was determined according to the method of Oyama and Eagle (*220*).
Testing schedule:
Day 0: Stock cells are diluted to 10–20 μg/ml (20,000–30,000 cells/ml) in complete medium. Cells are added to tubes and test material is added simultaneously or on day 1. Total volume is approximately 3–4 ml. A positive control is run with odd-numbered control groups.
Day 1: If 24-hour culture is used, it is refed and test material is added; protein values of base-line protein tubes are determined.
Day 3: Protein analyses of test, control, and at least three protein standard and medium blank control tubes are conducted.
Day 4: If 24-hour cultures are used, protein analysis as prescribed for day 3 is followed.
Dosage: Synthetics and plant products are tested by weight at 100, 10 and 1 μg/ml and crude fermentation products by dilution at 1:10, 1:100, and 1:1,000. Dried or crystalline fermentation products are also tested by weight at appropriate concentrations. Lower concentrations and all additional tests are to be done at five dose levels at 0.3-log intervals.
Quality control: Control tubes must show growth of at least six times that of base-line tubes. Positive control, 6-mercaptopurine (NSC-755), limits ED50 between 0.05 and 0.5 μg/ml.
Criteria of activity: By confirmation assays with synthetics and plant and animal extracts, ED50 ≤ 4 and ≤ 20 μg/ml, respectively.

B: TEST SYSTEMS USED IN THE SOVIET UNION

During the screening and detailed study of drugs with antitumor activity in vivo in the institutions of the Soviet Union, more than 30 model systems are used, including transplantable and spontaneous tumors of mice, rats, and rabbits. In addition, in some instances, studies are presented on the cytotoxic activity of drugs in vitro in different model systems.

Minor differences in methodology occur in the various institutions. Because of this, only general procedures are given for most of the methods used in obtaining the data. Nevertheless, the methodology is reflected in the tables and appendixes in accordance with the results obtained with the individual compounds.

Lymphoid Leukemia L1210

Origin

This tumor line originated as a lymphocytic leukemia in a DBA/2 female mouse in 1948 after the skin was painted with 0.2% 20-MCA in ethyl ether (*197*).

Source

L1210 strain was obtained from the NCI, Bethesda, Maryland, in September 1973.

General

Ascitic fluid is administered to DBA/2, BDF_1, or CDF_1 mice. Treatment begins 24–48 hours after transplantation. Route of administration depends on the drug and experiment.[2] The efficacy is evaluated by the life-span, and for kinetic studies of the effect of the drug, by an analysis of the kinetic curves of the alteration of the total number of leukemia cells (*147*).

Propagation of stock tumor

Animals: DBA/2 mice
Inoculum: Each mouse receives 0.25 ml of ascites tumor diluted with Hanks' solution in a ratio of 1:60.
Inplant site: ip
Time of transfer for propagation: 6–7 days
Transplantation for testing: Each mouse receives 10^5–10^6 leukemia cells in 0.1–0.3 ml of ascitic fluid diluted with sterile citrate in Medium 199 or physiologic solution.
Inoculation time: 6–7 days

Drug testing

Animals: BDF_1, CDF_1, or DBA/2
Weight: [3]
Age: [4]
Sex: [5]
No. of animals/test group: 6 (minimum 3)
No. of control animals/experiment: [6] 6–10
Testing schedule: Differs in accordance with purpose of test
Method of administering drug: Predominantly ip
Dosage: [7]

Evaluation

Acceptable control: Average life duration 7–9 days or 8–11 days, depending on quantity of grafted cells.
Parameter of effect: ILS% is compared with controls or number surviving to the 30th day.[8] In the kinetic study, the parameter of effect is the activity coefficient $N = \frac{\psi_c - \psi_t}{\psi_c}$, where ψ_c and ψ_t are the average specific rates of growth of the tumors in the control and treated groups (*147*).
Minimum criterion of activity: ILS by $\geqslant 25\%$
Day of final evaluation: The surviving animals are killed on the 30–90th day.

Lymphocytic Leukemia P388

Origin

This tumor line originated as a lymphocytic leukemia in a DBA/2 female mouse after the skin was painted with 3-MCA.

Source

The line was obtained from the NCI, Bethesda, Maryland, September 5, 1973 (*200*).

General

Ascitic fluid was administered ip to DBA/2 or BDF_1 or CDF_1 mice. Therapy begins 24 hours after inoculation.

[2] The treatment is given ip, iv, sc, or orally, depending on the properties of the drug and the purpose of the experiment.

[3] Minimal weight of mice is 20 g ± 3–4 g; minimal weight of rats is 90–120 g.

[4] Age of mice is 2–3 mo.; age of rats is 1.5–2 mo.

[5] Animals of the same sex were used for all experimental and control groups.

[6] No. of animals in control group depends on No. of experimental groups and is determined by the formula √No. of experimental animals × No. of animals in each experimental group.

[7] Dosage in the first experiment is selected at no less than three levels, which differ from one another severalfold. In subsequent experiments, doses are chosen in accordance with the results of the first experiment until the determination of the optimal dose.

[8] ILS% is calculated by the formula: average survival time in experimental group − average survival time in control group/average survival time in control group × 100.

Administration of drug [2]

Parameter of effect

Life-span

Propagation of stock tumor

Animals: DBA/2 mice
Inoculum: ip
Implant site: Ascitic fluid (0.25 ml/mouse) diluted 1:40 with Hanks' solution, ip
Time of transfer for propagation: 6–8 days
Transplantation for testing: DBA/2, BDF_1, or CDF_1 mice. Inoculation: Each mouse received 0.3 ml ascitic fluid diluted with citrate and Medium 199 containing 10^5–10^6 cells.
Inoculation time: 6–8 days

Drug testing

Animals: DBA/2, BDF_1, or CDF_1
Weight: [3]
Age: [4]
Sex: [5]
No. of animals/test group: 6 (3 for preliminary tests)
No. of control animals/experiment: [6] 6–10
Testing schedule: Differs, depending on purpose of experiment
Dosage: [7]

Evaluation

Acceptable control: Average duration of life, 8–11 days
Parameter of effect: ILS% of the controls or No. of survivors to 30th day of evaluation of effect [8]
Minimum criterion of activity: ILS $\geqq$ 25%
Day of final evaluation: Surviving animals were killed on 30–90th day.

Hemocytoblastosis La

Origin

Leukemia La was induced in C57BL mice by a single exposure to X-irradiation in 1955 (*221*).

Source

The La strain was obtained from Dr. Pujman of Czechoslovakia in 1960.

General

Transplantation is accomplished with a suspension of spleen cells containing a fixed quantity of leukemia cells. Treatment begins 24 hours after transplantation.

Administration of drug [2]

Parameter of effect

The duration of life is expressed as percent increase with respect to the controls as well as kinetic characterization.

Propagation of stock tumor

Transplantation for testing: Quantity of material transplanted and site of transplantation are indicated in tables (*see* Appendixes III, IV).
Transplantation time: 6–7 days

Drug testing

Animals: C57BL mice
Weight: [3]
Age: [4]
Sex: [5]
No. of animals/test group: 6–10 (minimum 3)
No. of control animals/experiment: [6]
Testing schedule: Differs depending on problems investigated
Method of administering drug: Predominantly ip
Dosage: [7]

Evaluation

Acceptable control: Average duration 6–9 days, depending on quantity of material inoculated
Parameter of effect: ILS% of controls or survival to 30th day, as well as coefficient of inhibition of leukemia process (N), showing how many times slower, compared with the controls, the leukemic process is developing.[8] $N = \frac{t_{exp}}{t_c}$, where t_{exp} and t_c are the times for reaching the same value of the magnitude being studied for the experimental and control groups (*147*).
Minimum criterion of activity: ILS by $\geqq$ 25%
Day of final evaluation: Surviving mice were killed on 30–90th day.

Lymphatic Leukemia L-5178Y

Source

This strain was obtained from the tumor bank of OSC AMS USSR.

General

L-5178Y is transplanted ip in hybrid mice. Treatment begins 24 hours after transplantation.

Administration of drug [2]

Parameter of effect

Inhibition of the development of ascites in terms of weight

Propagation of stock tumor

Inoculum: Each mouse receives ip 0.2 ml of ascitic fluid diluted with sterile physiologic solution containing 2×10^6 cells.
Time of transfer for propagation: 7 days

Drug testing

Animals: Hybrid mice
Weight: [3]
Age: [4]
Sex: [5]
No. of animals/test group: 8–10
No. of control animals/experiment: 10, calculated by formula [6]
Testing schedule: Differs depending on problems posed
Dosage: [7]

Evaluation

Acceptable control: Average volume of ascites on 10th day after transplantation is 6.8 ml.
Parameter of effect: Inhibition of development of ascites by weight [9]
Minimum criterion of activity: Inhibition of development of ascites by 50%

Ascites Tumor NK/Ly

Origin

Tumor NK/Ly was obtained in 1960 by transplantation from C3H mice with spontaneous lympholeukosis (*222*). Presently, NK/Ly represents a substrain of the Ehrlich tumor.

Source

Strain NK/Ly was obtained in 1962 from Hungary.

General

NK/Ly is transplanted with ascitic fluid ip into non-inbred mice. Treatment begins on the day after inoculation and is administered ip or sc.

Parameter of effect

Inhibition of growth of the tumor, ascites volume, or quantity of tumor cells.

Propagation of stock tumor

Inoculum: Quantity of inoculated tumor material and site of inoculation are indicated in Appendixes III, IV.
Time of transfer: 7–11 days

Drug testing

Animals: Non-inbred mice
Weight: [3]
Age: [4]
Sex: [5]
No. of animals/test group: 10–15
No. of control animals/experiment: 15–20, calculated by formula [6]
Testing schedule: Differs depending on problems posed
Dosage: [7]

Evaluation

Acceptable control: Average volume of ascitic fluid is 5–6 ml, or 2–2.5 ml of dense precipitate; average No. of tumor cells contained in peritoneal cavity of mouse is $250–400 \times 10^6$.
Parameter of effect: Percentage inhibition of volume of the ascitic fluid, or the dense precipitate, or in the No. of tumor cells [9]
Minimum criterion of activity: 100% inhibition when drug was injected ip; 40–60% inhibition for sc injection
Day of final evaluation: 8–12 days

Lymphosarcoma LI0-1

Origin

Lymphosarcoma LI0-1 was obtained in 1950 by transplantation of spleen from an AfB mouse with spontaneous leukemia (*222*).

Source

The tumor was obtained from the bank of the OSC AMS USSR.

General

The tumor is transplanted im in AfB mice or non-inbred mice. The treatment begins 24 hours or on the 4–5th day after transplantation.

Administration of drug [2]

Parameter of effect

Inhibition of tumor growth in weight

Propagation of stock tumor

Inoculum: Quantity of material transplanted and site of transplantation are indicated in Appendix III.
Transplantation time: 10–12 days

Drug testing

Animals: AfB or non-inbred mice
Weight: [3]
Age: [4]
Sex: [5]

[9] Percentage inhibition of tumor growth (by weight and volume of tumor, by volume of ascites, precipitate, or by quantity of tumor cells) is calculated by the formula: Percent inhibition = average index of tumor growth in control − average index of tumor growth in experimental group/average index of tumor growth in control × 100.

No. of animals/test group: 5–10
No. of control animals/experiment: [6] 12–15
Testing schedule: Differs, depending on problems posed
Dosage: [7]

Evaluation

Acceptable control: Average life duration is 10–18 days, average tumor weight on 11th day after transplantation is 2.9 g.
Parameter of effect: Percentage tumor growth inhibition in weight [9]
Minimum criterion of activity: Inhibition of tumor growth by ≧ 50% or minimum statistically significant percent of inhibition
Day of final evaluation: 11–12 days

Plasmacytoma MOPC-406

Origin

In 1967, the plasmacytoma was induced in a male BALB/c mouse with mineral oil plus immunization with bovine, sheep, horse, and swine erythrocytes (*224, 225*).

Source

Strain was obtained from Dr. M. Potter (United States) in 1971.

General

BALB/c or CDF_1 mice, preferably females, are administered ip a suspension of finely ground tumor nodules found in the peritoneal cavity along the mesenterium. Treatment begins 48 hours after transplantation.

Administration of drug [2]

Parameter of effect

Average life-span expressed in percent of the controls

Propagation of stock tumor

Animals: BALB/c, preferably females
Inoculum: A suspension of ground tumor nodules (0.2 ml/mouse) from the peritoneal cavity diluted with Medium 199 based on 1 g tumor tissue/10 ml medium
Implant site: ip
Time of transfer for propagation: 12–14 days
Transfer for drug testing: Same as for propagation (12–14 days)

Drug testing

Animals: BALB/c or CDF_1
Weight: [3]
Age: [4]
Sex: Preferably females
No. of animals/test group: 6–8
No. of control animals/experiment: 8–10, calculated by formula [6]
Dosage: [7]

Evaluation

Acceptable control: Average life-span is 15 days (13.2–17.1).
Parameter of effect: ILS% of controls or surviving mice [8]
Minimum criterion for activity: ILS by ≧ 25%
Day of final evaluation: 60–90 days

Lewis Lung Carcinoma

Origin

This tumor line arose spontaneously as a carcinoma of the lung in a C57BL mouse in 1951 (*203, 222*).

Source

The strain was obtained from the NCI, Bethesda, Maryland, September 1973.

General

A suspension of tumor tissue is transplanted sc in C57BL or BDF_1. Treatment begins 24–48 hours after transplantation.

Administration of drug [2]

Parameter of effect

Weight or volume of the tumor and life-span

Propagation of stock tumor

Animals: C57BL mice
Inoculum: Each mouse receives 0.5 ml of tumor suspension in Hanks' solution in a ratio of 1:2.
Implant site: im
Time of transfer for propagation: 11–12 days
Transfer for drug testing: Each mouse receives sc in the axillary region 0.5 ml of a tumor suspension in a dilution of 1 g tumor in 10 ml sterile Medium 199.
Transplantation time: 12–14 days

Drug testing

Animals: C57BL or BDF_1
Weight: [3]
Age: [4]
Sex: [5]
No. of animals/test group: 6
No. of control animals/experiment: [6] 12–14
Testing schedule: Differs, depending on purpose of experiment
Dosage: [7]

Evaluation

Acceptable control: Average weight of tumor on 13th day after transplantation, 4.3 g (3.5–7.4), average life duration, 24 days
Parameter of effect: ILS% of controls [8] or percent inhibition of tumor growth by weight or volume [9]
Minimum criterion for activity: Inhibition of tumor growth by ≧ 50% or ILS by ≧ 25%
Day of final evaluation: The surviving animals are killed on the 60–90th day.

Adenocarcinoma CA-755

Origin

CA-755 was obtained in 1936 from a spontaneous tumor of a mammary gland in a C57BL female mouse (*204*).

Source

The strain was obtained from the NCI, Bethesda, Maryland, September 5, 1973.

General

CA-755 is transplanted sc as a suspension of tumor tissue in C57BL or BDF_1 mice. Treatment begins 24–48 hours after transplantation.

Administration of drug [2]

Parameters of effect

Weight of tumor, volume of tumor, and life-span

Propagation of stock tumor

Animals: C57BL
Inoculum: Quantity of transplantable tumor material and site of transplantation are indicated in Appendixes III, IV.
Time of transfer for propagation: 12–14 days

Drug testing

Animals: C57BL or BDF_1 mice
Weight: [3]
Age: [4]
Sex: Only female
No. of animals/test group: 6–10
No. of control animals/experiment: 12–16, calculated by formula [6]
Testing schedule: Differs, depending on problems posed
Dosage: [7]

Evaluation

Acceptable control: Average tumor weight on 13th day after transplantation, 2.5 g (2.2–5.5 g); average life-span, 25.4 days. Growth rate of tumor depends on season. In the spring–summer period, life-span = 22.7 days, and a tumor weight at the time of death is 12.6 g; in the autumn–winter period, the life-span = 27.4 days, and an average tumor weight at the time of death is 9.4 g.
Parameter of effect: ILS% relative to controls,[8] or percent inhibition of tumor growth by weight or volume [9]
Minimum criterion for activity: Inhibition of tumor growth by ≧ 50–70% or ILS by ≧ 25%
Day of final evaluation: Surviving mice were killed on the 60–90th day.

Adenocarcinoma of Large Intestine AKATOL-1-71

Origin

In 1971, the tumor developed from a subcutaneous syngeneic transplant of embryonic large intestine in a BALB/c mouse (*226*).

Source

The strain was obtained in 1972 from the Laboratory of Virology of the OSC AMS USSR.

General

AKATOL is transplanted sc with a suspension of tumor tissue in BALB/c or CDF_1. Treatment begins 48 hours after transplantation.

Administration of drug [2]

Parameters of effect

Weight or volume of tumor and life-span

Propagation of stock tumor

Animals: BALB/c mice
Inoculum: Each mouse receives sc 0.5 ml of a suspension of tumor tissue diluted 1:2 with Hanks' solution.
Implant site: sc
Inoculation time: 18 days
Transplantation for testing: Each mouse receives sc in the axillary region 0.5 ml of a tumor suspension in a dilution of 1 g of tumor tissue in 10 ml of Medium 199.
Transplantation time: 18 days

Drug testing

Animals: BALB/c or CDF_1 mice
Weight: [3]
Age: [4]
Sex: [5]
No. of animals/test group: 6–12
No. of control animals/experiment: 12–14, calculated by formula [6]
Testing schedule: Differs, depending on problems posed
Dosage: [7]

Evaluation

Acceptable control: Average tumor weight on 13th day after transplantation, 1 g (0.85–1.5); average life-span, 57 days (44.2-82.6). Growth rate of tumor changes progressively from generation to generation.
Parameter of effect: ILS% relative to controls [8] or percent inhibition of tumor growth by weight and volume [9]
Minimum criterion for activity: Inhibition of tumor growth by ≥ 50% or ILS by ≥ 25%
Day of final evaluation: Surviving mice were killed on 90–100th day.

Carcinoma NK

Origin

Tumor arose in 1953 as a spontaneous undifferentiated carcinoma of the mammary gland in an H mouse.

Source

Strain was obtained from Hungary.

General

Tumor is transplanted sc in non-inbred mice. Treatment begins 1 day or 5 or 6 days after tumor transplantation.

Parameter of effect

Inhibition of tumor growth

Propagation of stock tumor

Inoculum: Quantity of transplanted material and site are indicated in Appendix III.
Time of transfer for propagation: 9–15 days

Drug testing

Animals: Non-inbred mice
Weight: [3]
Age: [4]
Sex: [5]
No. of animals/test group: 6–10
No. of control animals/experiment: 10, calculated by formula [6]
Testing schedule: Differs, depending on problems posed
Method of introducing drug: [2]
Dosage: [7]

Evaluation

Acceptable control: Average tumor weight on 13th day after transplantation is 5.2–5.8 g.
Parameter of effect: Percent inhibition of tumor growth by weight [9]
Minimum criterion for activity: Percent of growth inhibition = 50% or statistically significant percent of inhibition.
Day of final evaluation: 12–14 days

Squamous Cell Carcinoma of the Forestomach (PRZh)

Origin

In 1955, the tumor was induced with DMBA in the mucous membrane of the forestomach of C57Br mice (*227*).

Source

The tumor was obtained from the Strain Laboratory of the OSC AMS USSR in 1958.

General

PRZh is transplanted sc with a tumor suspension in mice of line C57Br. Treatment begins 48 hours after transplantation.

Administration of drug [2]

Parameter of effect

Weight or volume of tumor or life-span

Propagation of stock tumor

Animals: C57Br mice
Inoculum: Each mouse receives 0.5 ml of a suspension of tumor tissue diluted with Hanks' solution in a ratio of 1:2
Implant site: im
Time of transfer for propagation: 11–12 days

Drug testing

Animals: C57Br mice
Weight: [3]
Age: [4]
Sex: [5]
No. of animals/test group: 6–10
No. of control animals/experiment: 12–14, calculated by formula [6]
Testing schedule: Differs, depending on purpose of experiment
Dosage: [7]

Evaluation

Acceptable control: Average weight of tumor on 13th day after transplantation is 8.8 g (7.4–11.1).
Average life duration: 45 days (41–50.4)
Parameter of effect: ILS% or percent tumor growth inhibition in weight or in volume of tumor [8, 9]
Minimum criterion for activity: Inhibition of tumor growth by ≥ 50% or ILS by ≥ 25%
Day of final evaluation: Surviving mice were killed on 90th day.

Cancer of the Uterine Cervix RShM-5

Origin

In 1970, the tumor was induced with 3-MCA in a

subcutaneous autotransplant of the uterine cervix of a female CBA mouse (*228*).

Source

Strain was obtained in 1972 from the Endocrinology Laboratory of OSC AMS USSR.

General

RShM-5 is transplanted sc in a suspension of tumor tissue in mice of line CBA. Treatment begins 48 hours after transplantation.

Administration of drug [2]

Parameters of effect

Weight and volume of tumor and life-span

Propagation of stock tumor

Animals: CBA female mice
Inoculum: Each mouse receives sc in the axillary region 0.5 ml of a suspension of tumor tissue diluted with Hanks' solution in a ratio of 1 : 2.
Time of transfer for propagation: 18–21 days
Transfer for drug testing: Each mouse receives sc in the axillary region 0.5 ml of a tumor suspension in a dilution of 1 g of tumor in 10 ml of Medium 199.
Transplantation time: 21 days

Drug testing

Animals: Only CBA females
Weight: [3]
Age: [4]
No. of animals/test group: 6–10
No. of control animals/experiment: 12–14, calculated by formula [6]
Testing schedule: Differs, depending on problems posed

Evaluation

Acceptable control: Average weight of the tumor on the 13th day after transplantation is 0.75 g (0.56–1.0); average life-span is 43 days (39–54).
Parameter of effect: ILS% relative to control [8] or percent inhibition of tumor growth in weight and volume [9]
Minimum criterion for activity: Inhibition of tumor growth by $\geqq$ 50% or ILS by $\geqq$ 25%
Day of final evaluation: Surviving animals were killed on the 90–100th day.

B16 Melanoma

Origin

This tumor line arose spontaneously in 1954 on the skin at the base of the ear in a C57BL mouse (*199, 200*).

Source

The tumor was obtained in 1975 from the United States.

General

Melanoma B16 is transplanted sc with a tumor suspension in C57BL mice. Treatment begins 48 hours after transplantation.

Administration of drug [2]

Parameters of effect

Weight or volume of tumor and ILS

Propagation of stock tumor

Inoculum: Quantity of transplantable tumor material and site of transplantation are indicated in Appendix III.
Animals: C57BL mice
Time of transfer for propagation: 16–20 days

Drug testing

Animals: C57BL or BDF_1 mice
Weight: [3]
Age: [4]
Sex: [5]
No. of animals/test group: 6–10
No. of control animals/experiment: 12–14, calculated by formula [6]
Testing schedule: Differs, depending on problems posed
Dosage: [7]

Evaluation

Acceptable control: Average weight of tumor on 14th day after transplantation is 3.8 g (2.6–6.0); average life-span is 30–40 days
Parameter of effect: ILS% or percent tumor growth inhibition in weight and volume [8, 9]
Minimum criterion for activity: Inhibition of the growth of the tumor by $\geqq$ 50%, ILS by $\geqq$ 25–50%
Day of final evaluation: Surviving mice were killed on the 90th day.

Harding-Passey Melanoma

Origin

This tumor arose spontaneously in 1925 at the tip of the ear of a brown mouse (*229*).

Source

The Harding-Passey melanoma strain was obtained from the Tumor Bank of the OSC AMS USSR.

General

The tumor is transplanted sc in C3HA, BDF_1, or non-

inbred mice. Treatment begins on the 7–10th day after transplantation of the tumor.

Administration of drug [2]

Parameters of effect

Diameter and weight of the tumor and life-span

Propagation of stock tumor

Inoculum: Quantity of tumor material transplanted and the site of transplantation are indicated in Appendix III.
Time of transfer for propagation: 20–25 days

Drug testing

Animals: C3HA, BDF_1, or non-inbred mice
Weight: [3]
Age: [4]
Sex: [5]
No. of animals–test group: 10
No. of animals/control group:[6] 10–12
Testing schedule: Differs, depending on problems posed
Dosage: [7]

Evaluation

Acceptable control: Average tumor weight on 21st day is 2.5 g; average diameter is 1.7 cm.
Parameter of effect: ILS% or percent inhibition of tumor growth by weight and diameter [8, 9]
Minimum criterion for activity: Inhibition of tumor growth by $\geq$ 50%, ILS by $\geq$ 25%

Sarcoma 37

Origin

This tumor arose spontaneously in 1906 in an old female mouse as an adenocarcinoma of the mammary gland. In the process of transplantation, the tumor was transformed into an undifferentiated polymorphocellular sarcoma (*204*).

Source

Sarcoma 37 was obtained in 1958 from England.

General

The tumor is transplanted sc or ip with ascitic fluid in non-inbred mice. Treatment begins 24–48 hours or on the 5th day after transplantation.

Administration of drug [2]

Parameters of effect

Weight or volume of tumor, life-span, and volume of ascites (in ascitic variant)

Propagation of stock tumor

Inoculum: Quantity of transplanted tumor material and site of transplantation are indicated in Appendixes III, IV.
Time of transfer for propagation: 7–15 days

Drug testing

Animals: Non-inbred mice
Weight: [3]
Age: [4]
Sex: [5]
No. of animals/test group: 8–10
No. of animals/control group: Determined by formula [6]
Testing schedule: Differs, depending on problems posed
Dosage: [7]

Evaluation

Acceptable control: Average weight of tumor on 13th day after transplantation is 4.5–7.6 g, depending on season; volume of ascites is 4.0 ml; average life-span is 51.2 days.
Parameters of effect: ILS% and percent of tumor growth inhibition in weight and in volume [8, 9]
Minimum criterion for activity: Inhibition of tumor growth by $\geq$ 50% or increase in life-span by $\geq$ 25%
Day of final evaluation: Surviving animals were killed on 90–120th day.

Sarcoma AK

Origin

This tumor arose in 1946 as a polymorphocellular sarcoma after the injection of 9-dimethyl-3,4-benzacridine (*230*).

Source

The tumor was obtained from the Bank of the OSC AMS USSR.

General

Sarcoma AK is transplanted sc with a tumor suspension in mice of lines C57BL, A, AfB and non-inbred. Treatment begins 24 hours or on the 5th day after transplantation.

Administration of drug [2]

Parameter of effect

Inhibition of tumor growth or life-span

Propagation of stock tumor

Inoculum: Quantity of transplanted tumor material and site of transplantation are indicated in Appendix III.
Time of transfer for propagation: 10–14 days

Drug testing

Animals: Non-inbred mice
Weight: [3]
Age: [4]
Sex: [5]
No. of animals/test group: 6–10
No. of animals/control group: Calculated by formula [6]
Testing schedule: Differs, depending on problems posed
Dosage: [7]

Evaluation

Acceptable control: Average weight of tumor on 13th day after transplantation is 4.2–7.6 g.
Parameter of effect: Inhibition of tumor growth [9]
Minimum criterion for activity: Inhibition of tumor growth by ≧ 50% or minimal statistically significant percent of inhibition

Sarcoma 180

Origin

This tumor arose spontaneously in a male albino mouse in 1914 in the Crocker Institute in the United States. Originally, it was classified as a carcinoma, which was transformed in the process of transplantation into a poorly differential sarcoma (*204*).

Source

The tumor was obtained in 1975 from the United States.

General

Sarcoma 180 is transplanted sc with a tumor suspension in non-inbred mice. Treatment begins 48 hours or 5–6 days after transplantation.

Administration of drug [2]

Parameters of effect

Inhibition of tumor growth in weight and volume and life-span

Propagation of stock tumor

Inoculum: Quantity of transplanted tumor material and site of transplantation are indicated in Appendixes III, IV.
Time of transfer for propagation: 14–18 days

Drug testing

Animals: Non-inbred mice
Weight: [3]
Age: [4]
Sex: [5]
No. of animals/test group: 8–12
No. of animals/control group: 15–20, determined by formula [6]
Testing schedule: Differs, depending on problems posed
Dosage: [7]

Evaluation

Acceptable control: Average weight of tumor on 13th day after transplantation is 3.0 g (1.5–4.0); average life-span is 35 days (29.3–41.8).
Parameter of effect: ILS% or percentage inhibition of tumor growth in weight and in volume [8, 9]
Minimum criteria for activity: Inhibition of growth of tumor ≧ 50% or minimal statistically significant percent of inhibition and ILS ≧ 25%
Day of final evaluation: Surviving animals were killed on the 90th day.

Ehrlich Tumor

Origin

The initial tumor for the strain of Ehrlich solid adenocarcinoma was a spontaneous cancer of the mammary gland of mice that developed in 1905. The ascitic variant of Ehrlich tumor was obtained in 1932 by ip transplantations of Ehrlich solid adenocarcinoma (*204*).

Source

The Ehrlich tumor was obtained from the Bank of OSC AMS USSR.

General

The tumor is transplanted ip or sc with ascitic fluid in non-inbred mice. Treatment begins 24 hours after transplantation for the ascitic variant and in 4–6 days in sc transplantation.

Administration of drug [2]

Parameters of effect

Volume of ascites, weight of tumor, number of tumor cells, and life-span

Propagation of stock tumor

Inoculum: Quantity of transplanted tumor material and site of transplantation are given in Appendix III.
Time of transfer for propagation: 8–12th day

Drug testing

Animals: Non-inbred mice
Weight: [3]
Age: [4]
Sex: [5]
No. of animals/test group: 7–15
No. of animals/control group: 15–20, calculated by formula [6]

Testing schedule: Differs, depending on problems posed
Dosage: [7]

Evaluation

Acceptable control: On the 8–9th day, average volume of ascitic fluid is 7 ml; average number of tumor cells is 400×10^6; average weight of tumor is 2 g, average life-span is 12–20 days.
Parameters of effect: ILS% or percent inhibition of development of tumor growth according to volume of ascites, number of tumor cells, weight of tumor [8, 9]
In the kinetics study, the parameter of effect is the coefficient of activity $N = \frac{\psi_c - \psi_t}{\psi_c}$, where ψ_c and ψ_t are the average specific growth rates of the tumor in the control and experimental groups.
Minimum criterion of activity: Percent inhibition of tumor growth by $\geqq 50\%$ or ILS% by $\geqq 25\%$

Adenocarcinoma of the Mammary Gland

Origin

This tumor was transplanted from spontaneous tumor that developed in C3H mice by the time they were 8–10 months old (I–III generations of spontaneous tumor in this mouse line).

General

A suspension of crushed fragments of tumor tissue free of necrosis transplanted sc in C3H mice. Treatment ordinarily is administered ip.

Parameters of effect

Inhibition of tumor growth as calculated by the change in volume or weight of the tumor and increase in life expectancy of the animal receiving the drug compared with controls

Propagation of stock tumor

Animals: C3H mice
Transplantation material and site of transplantation: A suspension (0.2 ml) of crushed fragment of tumor tissue in physiologic solution is transplanted sc in the side of the mouse.
Inoculum: 50–70 mg
Transplantation time: Per strain and per experiment: 18–20 days

Drug testing

Animals: C3H mice
Weight fluctuation: 22–25 g
Age: Mice selected according to weight indicated
Sex: Males
No. of mice/test group: 10–12
No. of mice/control group: 15–20. In the kinetics study, 30–40 mice are in each control and experimental group; 3–5 mice are killed from each group at 2- to 3-day intervals, and the weight of the tumors in each group is determined.
Testing schedule: Day of tumor transplantation is day 0.
Method of administering drug: ip
Day of first injection of drug: Day 10–12 when tumor weight reaches approximately 200 mg
Dosage: Daily for 6–8 days or every other day, depending on the drug
Day of evaluation of effect: For determining the percent of inhibition of tumor growth, 40th day

Evaluation

Accepable control: Inhibition of tumor growth compared with controls [9]
Parameter of effect: Activity coefficient $N = \frac{\bar{\psi}_c - \bar{\psi}_t}{\bar{\psi}_c}$, where $\bar{\psi}_c$ and $\bar{\psi}_t$ are the average specific growth rates of the tumors in the control and treated groups of animals; determined in the kinetics study of the effect of the drug.
Minimum criterion for activity: Increase in average life-span of the treated animals compared with the controls [8]

Walker Carcinosarcoma 256

Origin

This tumor arose in 1928 as a spontaneous adenocarcinoma of the mammary gland of a pregnant unpedigreed rat (*204*).

Source

The strain was obtained from the tumor bank of the OSC AMS USSR.

General

The tumor is transplanted sc in non-inbred rats. Treatment begins 24 hours or 3–6 days after transplantation.

Administration of drug [2]

Parameters of effect

Inhibition of tumor growth in weight or size and ILS

Propagation of stock tumor

Inoculum: Quantity of transplanted tumor material and site of its injection are indicated in Appendix III.
Time of transfer for propagation: 7–14 days

Drug testing

Animals: Non-inbred rats
Weight: [3]

Age: [4]
Sex: [5]
No. of animals/test group: 8–12
No. of animals/control group: 15, calculated by formula [6]
Testing schedule: Differs, depending on purpose of experiment
Dosage: [7]

Evaluation

Acceptable control: Average weight of tumor on 14th day after transplantation is 33 g; average life-span is 15–25 days.
Parameters of effect: Percent of inhibition of tumor growth in weight or size and ILS% of controls [8, 9]

Coefficient of activity: $N = \frac{\bar{\psi}_c - \bar{\psi}_t}{\bar{\psi}_c}$, where $\bar{\psi}_c$ and $\bar{\psi}_t$ are the average specific growth rates of the tumor in the control and test groups.

Minimum criterion of activity: Percent inhibition of tumor growth $\geqq 50$ or minimal statistically significant percent of inhibition

Sarcoma 45

Origin

This spindle-cell sarcoma arose in 1949 as a result of the injection of DMBA into subcutaneous cellular tissue of a non-inbred rat (*231*).

Source

Sarcoma 45 was obtained from the tumor bank of the OSC AMS USSR.

General

The tumor was transplanted sc in non-inbred rats. Treatment begins on 4–5th day after transplantation.

Administration of drug [2]

Parameter of effect

Inhibition of tumor growth

Propagation of stock tumor

Inoculum: Quantity of transplanted tumor material and site of injection are given in Appendix III.
Time of transfer for propagation: 14–20th day

Drug testing

Animals: Non-inbred rats
Weight: [3]
Age: [4]
Sex: [5]
No. of animals/test group: 8–10
No. of animals/control group: 15, calculated by formula [6]
Testing schedule: Differs, depending on purpose of tests
Dosage: [7]

Evaluation

Acceptable control: Average weight of tumor on 16th day is 19.3 g; average life-span is 18-25 days.
Parameter of effect: Inhibition of tumor growth (weight) [9]
Minimum criterion for activity: Inhibition of tumor growth $\geqq$ 50–70% or minimal statistically significant percent of inhibition

Sarcoma M-1

Origin

Polymorphocellular sarcoma M-1 was obtained in 1943 from a tumor induced by 3,4-benzpyrene (*232*).

Source

Strain was obtained from the tumor bank of the OSC AMS USSR.

General

The tumor is transplanted sc in non-inbred rats. Treatment begins on the 5th day after transplantation.

Administration of drug [2]

Parameter of effect

Inhibition of tumor growth

Propagation of stock tumor

Inoculum: Quantity of transplanted tumor material and site of its injection are indicated in Appendix III.
Time of transfer for propagation: 14–16th day

Drug testing

Animals: Non-inbred rats
Weight: [3]
Age: [4]
Sex: [5]
No. of animals/test group: 8–10
No. of animals/control group: 10, calculated by formula [6]
Testing schedule: Differs, depending on problem
Dosage: [7]

Evaluation

Acceptable control: Average weight of tumor on 15th day after transplantation is 18 g; average life-span is 16–28 days.
Parameter of effect: Inhibition of tumor growth in weight, calculated by formula [9]

Minimum criterion for activity: Minimal statistically significant percent of inhibition

Jensen's Sarcoma

Origin

The polymorphocellular sarcoma arose in 1907 in a gray rat as a result of the injection of tuberculosis bacteria (*233*).

Source

The strain was obtained from the tumor bank of the OSC AMS USSR.

General

The tumor is transplanted sc in non-inbred rats. Treatment begins on the 1st or 5th or 6th day after transplantation.

Administration of drug [2]

Parameter of effect

Inhibition of tumor growth in weight

Propagation of stock tumor

Inoculum: Quantity of transplanted tumor material and site of injection are given in Appendix III.
Time of transfer for propagation: 10–14th day

Drug testing

Animals: Non-inbred rats
Weight: [3]
Age: [4]
Sex: [5]
No. of animals/test group: 8–10
No. of animals/control group: 10, calculated by formula [6]
Testing schedule: Differs, depending on problems posed
Dosage: [7]

Evaluation

Acceptable control: Average weight of tumor on 14th day after transplantation is 10.4–17.8 g; average life-span is 16–25 days.
Parameter of effect: Percent of inhibition of tumor growth in weight calculated by formula [9]
Minimum criterion for activity: Inhibition of tumor growth by $\geq 50\%$ or minimal statistically significant percent of inhibition

Sarcoma 536

Origin

The tumor strain was obtained in 1953 by transplantation of a spontaneously developed tumor in the abdominal cavity of a rat (*233*).

Source

The tumor was obtained from the All-Union Scientific Research Chemical-Pharmaceutical Institute.

General

This tumor is transplanted sc in non-inbred rats. Treatment begins on the 5–6th day after transplantation.

Administration of drug [2]

Parameter of effect

Inhibition of tumor growth in weight or life-span

Propagation of stock tumor

Inoculum: Quantity of transplanted tumor material and site of its injection are given in Appendix III.
Time of transfer for propagation: 12–14th day

Drug testing

Animals: Non-inbred rats
Weight: [3]
Age: [4]
Sex: [5]
No. of animals/test group: 8–10
No. of animals/control group: 10, calculated by formula [6]
Testing schedule: Differs, depending on problems posed
Dosage: [7]

Evaluation

Acceptable control: Average weight of tumor on 15th day after transplantation is 20–26 g; average life-span is 16–25 days.
Parameter of effect: Inhibition of tumor growth in weight calculated by formula [9]
Minimum criterion for activity: Minimal statistically significant percent of inhibition

Guerin Carcinoma

Origin

This carcinoma was obtained in 1934 by transplantation of a spontaneous adenocarcinoma of the uterus of a Wistar rat (*234*).

Source

The strain was obtained from the tumor bank of the OSC AMS USSR.

General

The tumor is transplanted as a suspension given sc to non-inbred rats. Treatment begins on the 3–7th day after transplantation of the tumor.

Administration of drug [2]

Parameter of effect

Inhibition of tumor growth

Propagation of stock tumor

Inoculum: Quantity of tumor material transplanted and site of inoculation are indicated in Appendix III.
Time of transfer for propagation: 13–17th day

Drug testing

Animals: Non-inbred rats
Weight: [3]
Age: [4]
Sex: Only females
No. of animals/test group: 10
No. of animals/control group: 15, calculated by formula [6]
Testing schedule: Differs, depending on purpose of experiment
Dosage: [7]

Evaluation

Acceptable control: Average tumor weight is 20–25 g.
Parameter of effect: Inhibition of tumor growth in weight [9]
Minimum criterion for activity: Percent of inhibition of tumor growth = 70.

Alveolar Liver Cancer RS-1

Origin

The tumor was induced in 1956 with acetylaminofluorene in a non-inbred rat. The initial tumor was a hepatocholangioma, now alveolar mucosal cancer (*235*).

Source

The tumor was obtained from the bank of the OSC AMS USSR.

General

The tumor is transplanted sc in non-inbred rats. Treatment begins on the 8–10th day after transplantation.

Administration of drug [2]

Parameter of effect

Inhibition of tumor growth in weight or size

Propagation of stock tumor

Quantity of transplanted material and site of injection are given in Appendixes III, IV.
Time of transfer for propagation: 25–30th day

Drug testing

Animals: Non-inbred rats
Weight: [3]
Age: [4]
Sex: [5]
No. of animals/test group: 8–10
No. of animals/control group: Calculated by formula [6]
Testing schedule: Differs, depending on problems posed
Dosage: [7]

Evaluation

Acceptable control: Average tumor weight on the 26th day after transplantation is 19 g; average life-span is 25–45 days.
Parameter of effect: Inhibition of tumor growth in weight [9]
Minimum criterion for activity: Inhibition of the tumor growth by $\geq 50\%$ or the minimal statistically significant percent of inhibition
Day of final evaluation: 18–20th day

Pliss Lymphosarcoma

Origin

The tumor was obtained in 1958 in the Research Institute for Oncology by G. B. Pliss, after sc transplantation of a tumor which arose in a rat that received 3,3-dichlorobenzidine. The tumor has been passed in non-inbred and albino rats in the Research Institute for Oncology since 1958 (*236*). The system is used as a model in which the parameter of effect is the weight of the tumors.

Propagation of stock tumor

The tumor is transplanted sc as 0.4 ml of a 30% suspension of tumor tissue in physiologic solution. The material for the transplantation is taken on the 14–16th day.

Drug testing

Transplantation site: sc on the flank, 0.4 ml of a 30% suspension of tumor tissue in physiologic solution, taken on the 14–16th day after transplantation
Animals: Albino, non-inbred rats raised by the Rappolovo Breeding Farm, males or females, weighing 100–120 g, aged 8–10 weeks
No. of animals/test group: 10
No. of animals/control group: 12–15
Testing schedule: Injections of drug given ip every day beginning with 4–5th day after transplantation, with a total of 10–12 injections
Dosage: A single optimal dose

Evaluation

On the day after completion of the therapy, according to the weight of the tumors

Acceptable controls: The acceptable average tumor weight in the controls is 12–15 g.
Parameter of effect: Percent inhibition of tumor growth [9]
Minimum criterion for activity: Inhibition of growth by 40–50%

Rhabdomyosarcoma MOP

Origin

Rhabdomyosarcoma MOP was obtained in the Research Institute for Oncology in 1947 by sc transplantation of a tumor which developed in a hind paw of a rat after the injection of 9,10-dimethyl-1,2-benzanthracene (*237*). The tumor was maintained in the laboratories of the Research Institute for Oncology by sc or im transplantation in non-pedigreed rats. The system is used as a model in which the parameter of effect is the inhibition of tumor growth.

Propagation of stock tumor

Animals: White cross-bred rats raised by the Rappolovo Breeding Farm
Inoculum: A 30% suspension (0.4 ml) of tumor tissue in sterile physiologic solution given sc
Time of transfer for propagation: The tumor for transplantation is taken from the animals on the 13–15th day.
Inplant site: The flank

Drug testing

Tumor site: Flank
Animals: Female albino cross-bred rats raised by the Rappolovo Breeding Farm, weighing 100–120 g, aged 6–8 weeks
No. of animals/test group: 10
No. of animals/control group: 15
Testing schedule: Injections of drug given ip daily, beginning with 3d–4th day after transplantation and continuing for 10 days
Dosage: One; occasionally several doses are used, consisting of 10–20% of the LD50

Evaluation

Acceptable control: Made on the basis of the weight of the tumors on the day following the completion of therapy; acceptable average weight of the tumor in the controls is 15 g.
Parameter of effect: Percent inhibition of tumor growth [9]
Minimum criterion for activity: Inhibition of tumor growth by 90–100%

Ovarian Tumor OYa

Origin

Ascites tumor of the rat ovary OYa was obtained in 1958 by transplantation of an ovarian tumor, which arose in a rat whose mother had received DMBA during the period of gestation and lactation (*238*).

Source

The strain was obtained from the OSC AMS USSR in 1962.

General

The strain was passed ip in albino rats raised by the Rappolovo Breeding Farm. The system is used as a model in which the parameter of effect is the inihibition of tumor growth.

Propagation of stock tumor

Animals: Albino rats from Rappolovo Breeding Farm
Inoculum: Ascitic fluid (0.4 ml) obtained on the 8–10th day after transplantation
Inplant site: ip

Drug testing

Implantation site: Ascitic fluid (0.4 ml) obtained on the 8–10th day after transplantation, ip
Animals: Albino non-inbred female rats weighing 100–120 g
No. of animals/test group: 10–12
No. of animals/each control group: 10–12
Testing schedule: Injections, ip or sc, of drug for 7–8 days beginning with the first day after transplantation
Dosage: Ordinarily, a single optimal dose is used with the different routes of administration of the drug.

Evaluation

On the day following the completion of therapy, according to the total volume of ascitic fluid [9]
Acceptable control: Average quantity of ascitic fluid acceptable for control is 30–40 ml.
Minimum criteria for activity: For ip injections, 70–100% inhibition; for sc injections, 40%.

Brown-Pierce Epithelioma

Origin

This line was obtained in 1921 from an undifferentiated tumor (possibly epithelial originally) of the scrotum of a rabbit (*204*).

Source

The tumor strain was obtained in frozen form from the OSC AMS USSR.

General

The system is used as a model for which the chief parameters of response are the percent of inhibition and retardation of metastasis into the other organs.

Procedure

Minced tumor diluted with physiologic solution was given intratesticularly in doses of 0.4–0.5 ml.

Propagation of stock tumor

Animals: Male rabbits
Inoculum: The tumor suspension of the Brown-Pierce epithelioma is injected in a quantity of 0.5 ml.
Implant site: Right testis
Time of transfer for propagation: Days 20–21
Time of transfer for drug testing: Days 20–21

Drug testing

Animals: Male rabbits
Weight: 300 g, with minimum weight of 250 g
Age: Usually 7–8 months
No. of animals/test group: 10
No. of animals/control group: No less than 10
Testing schedule: Indicated in Appendix III

Evaluation

Efficacy of a drug was evaluated according to a four-point system with subsequent derivation of an arbitrary (average) index of metastatic activity for each organ in the experimental and control groups. On the basis of a comparison of the sum of these indexes (for all organs) in treated and control animals, the percent of inhibition of the metastasizing process was determined and compared with the results obtained with other antitumor drugs.

Sarcoma 37, Tumor L-5178Y, Ehrlich Tumor, Tumor NK/Ly

Substrains

Adapted to growth in vitro

Origin

Sarcoma 37 (ascites) was adapted to growth in vitro by means of repeated passages of the ascites tumor cells in the form of suspension cultures in test tubes and in the peritoneal cavity of animals. With this method of selection, tumor cells were obtained that preserved their malignancy and their ability to reproduce in vitro. In this way, a substrain of sarcoma 37 was obtained that was capable of regular growth in primary suspension cultures. The strain was maintained by transplantation in animals with periodic (twofold to threefold) passage through an in vitro/in vivo system every 3–4 months (*239*). Besides the substrain of sarcoma 37 described above, use was made of the tumors L-5178Y, Ehrlich tumor, and NK/Ly, which are also adapted to growth in vitro.

Source

Substrains of sarcoma 37, tumor L-5178Y, Ehrlich tumor, and NK/Ly were obtained in 1973 from the Institute for the Search for New Antibiotics of the AMS, USSR.

Strain transplantation

Animals: Non-inbred mice
Age: 2–3 months
Transplantation: Each mouse is given injections of 5×10^6 cells in 0.5 ml of physiologic solution.
Implant site: ip
Time of transplantation: 5–6th day

Drug testing

The tumor cells removed directly before the experiment from the abdominal cavity of the mice are introduced into a test tube containing medium and incubated with the drug at 37° C for 20 hours. The incubation medium is 50% Eagle's Basal Medium and 50% hydrolysate of 0.5% lactalbumin in Hanks' solution with the addition of 20% bovine serum and 0.1 mg streptomycin/ml of medium. The number of tumor cells/milliliter of medium is 4×10^5. The drug concentrations tested are 100, 50, and 10 μg/ml in one of the following solvents: alcohol, dimethyl sulfoxide, polypropylene glycol, acetone, 1% Na_2CO_3 solution, or 1% tartaric acid solution. The concentration of the solvent should not exceed 10%. If activity is detected at the lowest concentration, then lower concentrations are tested. The number of samples in the controls without incubation (initial control) is 6; in the controls after incubation (incubator control), 6; for each concentration of the drug, 2. The number of concentrations of each drug tested is 3.

Criteria of culture growth and cytotoxic activity of drugs

The evaluation of the growth of the cultures and the cytotoxic activity of the drugs is conducted by spectrophotometric determination of the total DNA and RNA content by the method of extinction difference (*240*). For this, after preliminary washing of the centrifuged cell precipitate (to free it of acid-soluble compounds) with cold 0.2 N $HClO_4$ and subsequent hot acid hydrolysis in 0.5 N $HClO_4$ at 90° C for 20 minutes, the OD of the hydrolysate is determined at wavelengths of 270 and 290 nm. The content (sum) of DNA and RNA is calculated by the formula: Σ NA (μg/ml) = OD at 270 nm − OD at 290 nm/0.19 × 10.8, where 0.19 and 10.8 are the average coefficients for converting the nucleic phosphorus to the quantity of nucleic acid. The intensity of the culture growth is determined by the increment of the sum of nucleic acids according to the formula: Percent culture growth intensity = $\Sigma\ NA_{incubated} - \Sigma\ NA_{initially} / \Sigma\ NA_{initially} \times 100$, where $\Sigma\ NA_{incubated}$ is the sum of nucleic acids in the incubator control, and $\Sigma\ NA_{initially}$ is the sum of nucleic acids in the initial control.

Evaluation

Acceptable control: Increase in the sum of nucleic acids ≧ 40%

Criterion of cytotoxicity: ED50 is the dose suppressing the synthesis of nucleic acid by 50%.

Cell Line CaOV

Origin

The primary culture was obtained in the OSC AMS USSR in June 1959 from tissue of a cystadenocarcinoma of a human ovary (*241*).

Source

The cells of line CaOV are maintained in the form of a monolayer culture at the OSC AMS USSR, and the material is also stored in their cell bank.

General

Reinoculation procedure: Cells are detached by a 0.25% solution of trypsin in phosphate buffer, then the collected culture is reinoculated once weekly in a ratio of 1 : 2. The nutrient medium is a synthetic Medium 199 with 10% bovine serum and 50 IU kanamycin/ml. Culture is kept in the incubator at 37° C.

Preparation of cultures for experiment

Material for inoculation: Cells detached from the glass are diluted with prepared nutrient medium to a density of about 1×10^5 cells/ml.

Preparation for cultures: The cells are inoculated in standard flat-bottomed vessels with a volume of 10 ml and a bottom diameter of 20 mm. Rubber test tube stoppers were of nontoxic material. Two milliliters of the cell suspension is inoculated with a total of about 2×10^5 cells.

Study of drugs

Selection of cultures for tests: Cultures are selected with the same pink color of the nutrient medium; 1-day-old cultures are used.

No. of cultures in experimental group: From 2 to 6; usually 3–4; a group of cultures with the same concentration of one substance being tested is considered as the experimental group. No. of control cultures in one series of experiments depends on the No. of experimental groups and No. of cultures in each group, usually from 8 to 12.

Testing schedule: A single addition to a 1-day culture of 1 ml of a solution of the substance being studied in a protein-free nutrient Medium 199; exposure to substance is for 48 hours.

Concentration of substance being studied: Successive dilutions of the substance are used with a final concentration of 100, 10, and 1 μg/ml. A weighed portion of the substance (up to 10 mg) is dissolved in 2 drops of DMSO, with subsequent dilution with Medium 199.

Effect evaluation: The effect is evaluated according to: 1) change in the incorporation of [^{3}H]dThd by the cells, 2) change in the total content of nucleic acids in the cells, and 3) change in the total content of protein in the cells.

Determination of level of incorporation of [^{3}H]dThd by the cells: By the end of the exposure period to the drug, the nutrient medium is replaced with fresh medium containing [^{3}H]dThd in the concentration of 1 μ/ml. Exposure is for 1 hour, after which the cultures are cooled to 0° C, the medium decanted, the cells washed twice with chilled Hanks' solution and once with chilled 2.5% perchloric acid solution in distilled water. Nucleotides are hydrolyzed and extracted in 5 ml of 10% perchloric acid in distilled water in a water bath at 80° C for 20 minutes. To 10 ml of standard dioxan scintillation liquid (ZhS-8), 0.5 ml of extract is added, and, after neutralization with 0.1 ml ammonia, measurement with a liquid scintillation counter is made of the average value of the radioactivity level for the control and for each of the experimental groups.

Determination of the total content of nucleic acids in the cells: The nucleotides remaining in the samples of 4.5 ml of extract in 10% perchloric acid are used for the spectrophotometric determination of the total content of nucleic acids in the cells. The extinction of the extract is determined at wavelengths of 270 and 290 nm. On the basis of the extinction difference, according to Spirin's formula (*240*), determination is made of the total content of nucleic acids in the culture.

Determination of the total protein content in the cultures: After removal from the specimens of the nucleotide extract, the remaining cells are used to determine the quantity of protein in them. The cells are lysed at 37° C with a 1 N solution of NaOH in distilled water. Protein is determined by Lowry's method (*242*).

Processing of results: For each criterion of evaluation, the ratio in percent of the average index is calculated for each experimental group relative to the control. On the basis of the magnitudes obtained by probit analysis, the ED50 value is determined, as applicable to each evaluation criterion.

Minimal activity criterion: The drug is considered active if the ED50 is lower than 100 μg/ml for one of the evaluation criteria.

Simultaneously, with the study of the biologic activity of the unknown substance, a structurally similar substance with a known cytotoxic effect was used as a positive control.

Chapter III: Analysis of Experimental Data and Correlations With Clinical Use of Drugs[1]

A: COMPARISON OF SYSTEMS FOR STUDYING ANTITUMOR DRUGS IN THE UNITED STATES AND SOVIET UNION

As a result of our parallel study of drugs, a large body of factual material has been obtained that can be subjected to analysis to find the most informative test systems and to establish correlations with the data from clinical research.

However, to conduct such an analysis, it is first necessary for us to determine whether the data obtained in different countries are comparable and whether the totality of the available data in the cooperating countries can be used. For this purpose, a compilation was made of the results of exposure of identical tumors to the same drugs when they were studied in the United States and Soviet Union. When this was done, the data obtained were indeed comparable (table 3). Differences noted in a number of instances in the magnitude of the responses for the same drugs administered in treatment of the same tumors may be accounted for by variations in therapeutic schedules and the extent of fluctuation ordinarily observed in the activity of drugs in various experiments. Consequently, it appeared justifiable to combine the material obtained in both countries and to discuss the data as a whole.

Since one of the primary objectives of this investigation was to study the possibility of transferring experimental data to clinical use, it was considered essential to supplement the list of agents with a number of characterized, clinically active drugs. Twenty-four such drugs (table 4) studied in the experimental tumor models most frequently used for screening were selected for this purpose.

Table 5 presents summary data on the antitumor activity of 71 drugs in the study. The antitumor activity is expressed in arbitrary units based on a summary evaluation of efficacy. Taken into consideration were the response parameters, ILS of the treated animals, and inhibition of tumor growth. For convenience of discussion, the drugs are grouped in accordance with similarity in chemical structure or mechanism of action. In addition, data in table 6 indicate the effect of the drugs on the life-span of the treated animals. The results of clinical study of many of the same compounds (*5, 243–250*) are given in table 7.

Different models and methods are used in the various institutions of the United States and the Soviet Union that are engaged in experimental studies of antitumor properties of certain substances. However, the basic material summarized in the present monograph is the result of the study by the NCI (all the substances cited in this volume were studied under the auspices of this Institute) and the OSC of the USSR Academy of Medical Sciences (almost 90% of the drugs were studied at the OSC and the remainder at cooperating institutions). Therefore, it was considered possible that a comparison of the methods of drug screening could be made with materials at these two institutions and, when necessary, with the data from other institutes of the USSR.

Models

Certain common model systems have been used by the NCI and OSC in the study of the antitumor activity of drugs: leukemias L1210 and P388, LL, and melanoma B16. All four tumor models are incorporated in the screening program at the NCI but at the OSC, although leukemia L1210 and LL are used regularly, P388 and B16 are supplementary models reserved for in-depth study of active drugs.

The assortment of experimental tumors that are used in the study of antitumor drugs in both countries is large. However, the decision concerning the development of drugs in the NCI has been based largely on the results with five experimental systems: L1210 (ip), L1210 (sc), P388, B16, and LL. Ependymoblastoma inoculated ic has often been included. In the detailed investigation of active drugs, numerous other animal tumors have also been used. In a new prospective screen, use is being made of the murine intestinal tumors, colon 26 and colon 38; mouse mammary gland carcinoma, $CD8F_1$; and human colon, breast, and lung tumors growing in athymic mice. However, data on these tumors are not presented here because of the small volume of studies conducted at this time.

To determine the antitumor activity of drugs, the OSC uses tumor models L1210 (ip), hemocytoblastosis La, mammary gland adenocarcinoma Ca-755 and LL. These tumors constitute the primary system of screening for

Abbreviations: LL = Lewis lung (tumor); BCNU = 1,3-bis (2-chloroethyl)-1-nitrosourea; CCNU = 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea; 5-FU = 5-fluorouracil; PCNU = 1-(2-chloroethyl)-3-(2,6-dioxo-3-piperidyl)-1-nitrosourea; ara-C = cytosine arabinoside; Me-CCNU = 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea; ILS = increase in life-span; NCI = National Cancer Institute; OSC = Oncological Scientific Center; DTIC = dacarbazine; MNU = methylnitrosourea; *cis*-PT(II) = *cis*-platinum(II) diamminedichloride; ic = intracerebral(ly); LD50 = mean lethal dose; HGPRT = hypoxanthine-guanine phosphoribosyltransferase; ED50 = median inhibitory concentration.

[1] This chapter was prepared by Zoya P. Sof'ina, Abraham Goldin, and A. K. Belousova.

TABLE 3.—*Comparison of results of antitumor activity of drugs in the USSR and the United States*

Drugs	Tumors	USSR				United States			
		Route of administration	Days after tumor inoculation	Dose, mg/kg	ILS%	Route of administration	Days after tumor inoculation	Dose, mg/kg	ILS%
Dopan	L1210	ip	1–8	0.4	63	ip	1–death	2	70
	LL	"	2, 6	0.4	0	"	1–9	1	26
Fluorodopan	L1210	Oral	"	60	18	Oral	1, 9 every 3 hr	32	31
	LL	"	"	60	10	ip	1, 5, 9	23	22
Sarcolysin	L1210	ip	"	7	107	"	1–10	8	91
	LL	"	2–6	2	45	"	1–11	1	10
Asaley	L1210	Oral	2, 6	120	35	"	1, 5, 9	64	58
	LL	"	2–6	40	22	"	1–9	4	24
Phenestrol	L1210	sc	"	100	14	sc	1	100	2
Distron	L1210	"	2, 6	400	41	ip	1–9	200	15
	LL	"	2–6	25	27	"	"	50	21
Palphicerin	L1210	"	"	25	18	sc	"	100	36
	LL	"	"	25	3	ip	"	12.5	0.4
Prospidine	L1210	ip	1–5	200	0	"	"	132	0.7
Ftorafur	L1210	"	1, 5, 9	500	80	"	1, 5, 9	833	88
Carminomycin	L1210	"	2, 6	0.6	38	"	1	0.65	53
		"	"	0.5	21	"	1–9	0.03	3
Chanerol	L1210	"	2–6	10	15	"	1–5	2.2	8
	LL	"	"	10	7	"	1–17 every other day	8	5
Colchizin	L1210	"	2, 6	100	0	"	1–5	200	18
	P388	"	1–8	120	157	"	1–9	200	70
	LL	"	2–6	120	7	"	"	100	2
Diazan	L1210	sc	1, 3, 5, 7	10	30	"	"	6.3	41
	P388	"	1, 4, 7, 10	25	85	"	"	3	70
Variamycin	L1210	ip	1–6	1	0	"	"	0.75	15
	P388	"	"	1	95	"	"	1.5	70
Reumycin	L1210	"	1–9	2.5	10	"	"	0.75	4
	P388	"	"	2.5	11	"	"	3	0
Agavoside	L1210	"	1–5	5	12	"	"	1.3	3
Digitonin	L1210	"	1–7	6	0	"	"	40	2
	P388	"	1–5	15	12	"	"	0.62	1
Cyclophosphamide	L1210	"	2, 6	100	117	"	5	172	224
	LL	"	4, 18	200	90	"	8	300	71
BCNU	L1210	"	2, 6	35	700	"	1	30	206
	LL	"	4, 11	40	20	"	1	40	39
CCNU	L1210	"	2	40	419	"	5	50	179
	LL	"	4	50	16	"	1–9	2	7
TIC-mustard	L1210	"	2–7	150	120	"	"	87	143
	LL	"	2, 6	120	30	"	8–16	50	23
Streptozotocin	L1210	"	2–6	50	28	"	1–9	50	38
	LL	"	"	50	0	"	8–16	20	15
Hexamethylmelamine	L1210	"	"	70	13	"	1–9	150	24
	LL	"	"	125	18	"	"	50	68
5-FU	L1210	"	2–11	20	84	"	"	16	73
	LL	"	2–6	26	0	"	8–16	20	32
Cyclocytidine	L1210	"	1–8	100	127	"	1–9	300	160
	LL	"	2–6	120	3	"	"	640	35
Azacytidine	L1210	"	1–9	3	136	"	"	3	124
Guanazole	L1210	"	"	1,800	61	sc	1, 5, 9 every 3 hr	600	226
	LL	"	2–6, twice daily	500	4	ip	8–16	800	54

TABLE 3.—*Comparison of results of antitumor activity of drugs in the USSR and the United States (continued)*

Drugs	Tumors	USSR				United States			
		Route of administration	Days after tumor inoculation	Dose, mg/kg	ILS%	Route of administration	Days after tumor inoculation	Dose, mg/kg	ILS%
Gallium nitrate	L1210	"	2–6	60	8	"	1–9	50	15
S-Trityl-L-cysteine	L1210	Oral	"	200	37	"	"	70	55
Inosine diglycolaldehyde	L1210	ip	1–5	100	32	"	"	200	75
	LL	"	2, 6	200	5	"	1–11	65	15
	P388	"	2, 6, 10	200	104	"	1–10	150	109
Ellipticine	P388	"	1, 4, 7	30	60	"	"	25	104
3-Deazauridine	L1210	"	2–6	500	41	"	1–9	200	50
6-Selenoguanosine	"	"	"	30	63	"	"	25	129
ICRF-187	"	"	"	400	96	"	2, 5, 9	1,024	86
Chlorozotocin	"	"	"	7.5	156	"	1	30	517
PCNU	"	"	1–5	2	109	"	2	6	103
Nordopan	"	"	"	0.4	55	"	1–death	0.3	59
Quinoline derivative	"	"	2–6	10	483	"	1, 5, 9	25	201
α-Deoxythioguanosine	"	"	"	80	54	"	1–3	40	78
Townsend's nucleoside derivative	"	"	"	15	63	"	1–9	25	74

drugs. In the second step of the study, AKATOL adenocarcinoma of the large intestine, cancer of the uterine cervix RShM-5, squamous cell forestomach cancer PRZh, and plasmacytoma MOPC-406 are used more often than others. For promising substances, this assortment of tumors is usually supplemented by various other experimental models. Hormone-sensitive tumors and endocrinologic tests are used for drugs with presumed hormone activity. Immunoactive drugs are studied with immunologic test sytems.

Schedules of Drug Application

Studies of antitumor effect at the NCI and OSC differ also in the schedules of application of the drugs being investigated. At the NCI, the effect of the drugs is studied on various schedules: daily, single, and intermittent (with an interval of 96 hr) administration. The duration of the course in multiple administration is usually 9 days. At the OSC, compounds are usually introduced during screening in the form of a brief 5-day course (every day or twice at an interval of 96 hr). In other institutions of the Soviet Union longer courses of therapy are administered ordinarily.

A comparison of the results of studies of the same drugs on the same model systems in the United States and Soviet Union shows that when the treatment of the animals was begun at the same time after transplantation of the tumor, differences in the schedules of drug application most often did not result in marked variations in antitumor effect (table 3). The difference in the degree of effect is significant only when the antitumor effect of the drug depends primarily on the schedule of therapy. Thus when tested on mice with L1210 at the OSC, the effect of guanazole was substantially lower than at the NCI (a 61% ILS on a daily schedule as opposed to a 226% increase on an every 3-hour intermittent schedule, respectively). The effect of this drug is S-phase-specific, as a result of which one drug injection/day is insufficient for the maximum possible suppression of the growth of tumors with a high proliferative pool and a short generation time (12 hr). Difference in magnitude of the effect was also found in the testing of other drugs (6-selenoguanosine, Cain's quinoline derivative, chlorozotocin, BCNU, or CCNU), which require either prolonged daily administration or infrequent injection of massive doses

TABLE 4.—*Drugs with known clinical activity included in discussion*

Methotrexate	Prednisolone (prednisone)
6-Mercaptopurine	Chlorambucil
6-Thioguanine	Vinblastine
Ara-C	Mithramycin
Hydroxyurea	Daunorubicin
Dactinomycin	Bleomycin
Adriamycin	Mitomycin C
Vincristine	Me-CCNU
Procarbazine	Dibromodulcitol
Nitrogen mustard	L-Asparaginase
Estracyt	Dibromomannitol
Myleran	Thio-TEPA

TABLE 5.—*Effect of drugs on experi-*

Drug	Leukemias								Lymphomas					Plasma-cytomas					
	L1210	P388	La	L-5178Y	L-AK	Friend's virus leukemia	Lymphocytic leukemia P-288	P1534	Lymphosarcoma P1798	Pliss	LI0-1	Mecca	Gardner	MOPC-406	LPC-1	Adenocarcinoma Ca-755	Lewis lung	AKATOL-1-71	RShM-5
Methotrexate	+++	+++	−											+		+++	+	+++	++
Tomizin	−	−	−														−		
Quinoline derivative	+++	+++	+++													+	−	++	++
5-FU	++	+++	+++							−				++		+++	++	−	−
Ftorafur	++	+	++											+		++	+++	+	+
3-Deazauridine	+	−	−													++	−		++
Ara-C	++	+++	−											−		−	++	+	++
Cyclocytidine	+++	+++	+											−		++	++	+	+
5-Azacytidine	+++	+++	++	+	+									++		+++	++	+++	−
6-Mercapto-purine	+	+	−											++		+++	−	+++	−
6-Thioguanine	++	++	−											++		+++	−	+++	+
α-Deoxythio-guanosine	++	++	−		+											+++	−	+	−
6-Seleno-guanosine	+++	++	−										+++			+++	++	++	++
Inosine digly-colaldehyde	+++	+++	+++		+++									+		−	−	−	−
Townsend's nucleoside derivative	+++	−	−													−	−	+++	++
DTIC	+	++	−											−		+	+	++	+
Reumycin	−	−		++												+	−		
Hydroxyurea	+	++	+++											+		++	++	+++	+++
Guanazole	+++	+	+++		+++									+		+++	++	++	+++
ICRF-187	+++	++	−													+++	++	+	+
Dactinomycin	+	+++	+++											++		++	−	+	++
Adriamycin	++	+++	+++											++		+++	−	+	−
Carminomycin	++	++	+++								+++			+		+	+	+	++
Olivomycin	++	+++	++								++					+++	−	+	
Variamycin	−	++	++								+					+			
Aton	−	−														+			
Vincristine	−	+++	++											−		++	−	+	++
Colchizin	−	+++	+++											+		+++	−	++	+
Chanerol	−	−	−													+++	+	++	+++
Glucomannan	−	−														+	++	+	+
Agavoside	−	−														+	+	+	+
Digitonin	−	−	+++													+	−		−
Funkioside	−	−	++													+	++	++	+
Vitalboside	−	−	+++													++	−	+	
Coralyne sulfoacetate	++	++															++	++	+
Ellipticine	+++	+++			+												−	−	−

mental tumors of mice and rats [a]

Carcinomas										Ependymoblastoma	Melanomas		Sarcomas and undifferentiated tumors							
PRZh	Ca-1025	Carcinoma NK	Ca Guerin	Rhabdomyosarcoma MOP	Ovarian tumor (OYa)	Ca-C3H	Hepatoma 129	Alveolar liver cancer (RS1)	Walker 256		B16	Harding-Passey melanoma	Ehrlich's ascites tumor	Ascites tumor NK/Ly	Sarcoma 37	Sarcoma 180	Sarcoma 536	Sarcoma AK	Sarcoma 45	Sarcoma M-1	Jensen's sarcoma
−											+++				+	+					
		−						−		−	+++		++	++	++	+	−	+		+	+
−											−		−								
−										+	++				+	−					
		+						+	+	−	+	+			++	+		+	−		−
											−										
−											++				+	−					
										−	−				+						
−							−				++				+	−					
+											++				−	−					
++											+				++	−					
											+										
											++										
										−	−				−	−					
											−										
−											+++				−						
			−						−		−	+	+		+	−					
											++				++	+					
−										+	++				+	−					
+										+	+										
+											+				+	−					
−											+				+	−					
+											−			++	+	++					
											+					+					
			+						+		+	+	−		+	+			+	+	
										−	−				−						
−											+				+						
+											+				+	−					
+											−				++	−					
−											−				−	+					
+										−	+										
										−	+				+						
											+				+						
											+										
											+										
										−	++										

TABLE 5.—*Effect of drugs on experi-*

Drug	Leukemias								Lymphomas					Plasma-cytomas					
	L1210	P388	La	L-5178Y	L-AK	Friend's virus leukemia	Lymphocytic leukemia P-288	P1534	Lymphosarcoma P1798	Pliss	LI0-1	Mecca	Gardner	MOPC-406	LPC-1	Adenocarcinoma Ca-755	Lewis lung	AKATOL-1-71	RShM-5
Dichloroallyl lawsone	−	++															−	+	−
Indicine-*N*-oxide	+	+++															+	+	−
Nitrogen mustard	+	++	+											+		−	−	+	−
Nordopan	++	+++	+++													+++	++	+++	+
Dopan	++	++	++										++	+		−	++	−	−
Fluorodopan	+	++	−										−	−		++	++	+++	−
Sarcolysin	+++	+++	+++		++							+++	++	++		+++	+++	+	+++
Asaley	++	++	++											+		+++	++	+	++
Spirohydantoin mustard	++	+++	++													+	++		+
TIC-mustard	+++	++	+		++											+	++	−	+
Palphicerin	+	+++	−											+		+++	−	+	+++
Prospidine	−	++	−								−					++	++	++	+
Cyclophos-phamide	+++	+++	+++		+++	+++	+++	++	+				+++	+++	+++	+++	+++	+++	+++
Phenthyrine	−	+	−											−		+++	++	−	+
Estracyt	−		−											−		−	−		−
Phenestrol	−	−	−													+	−		−
Distron	+	++	++											−		+++	+	+	++
Fotrin	++	+++	+++								++						−		−
Dioxadet	+++	+++								−	−						−		
Diiodobenzo-tepa	++	+++															−		
Hexamethyl-melamine	+	−	+											−		+++	+++	+	++
MNU	+++	+++	+													++	++	++	+
BCNU	+++	+++	−		+											++	+++	+++	+++
CCNU	+++	+++	−		+									−		+	+++	++	+
PCNU	+++	+++	−													++	+++	++	++
Streptozotocin	+	++	+++											+		−	−	++	+
Chlorozotocin	+++	+++	−													−	++	++	+++
Diazan	+	++	+++													+			
Myleran	−	−	−											−		+	−	+	
Cain's acridine derivative	++	+++	−													++	++	+	++
cis-Pt(II)	++	+++	+++		++									−		+++	++	+++	−
Gallium nitrate	−	+	+++		−									−		+++	−	++	−
S-Trityl-L-cysteine	++	+++			+											+	−		
Prednisolone (prednisone)		−	−													++	−	+	−
Procarbazine	++	++	−											−		++	−	+++	−

[a] − = absence of effect; + = ILS by 25–49% or inhibition of tumor growth by 50–74%; ++ = ILS by 50–99% or inhibition of

mental tumors of mice and rats [a] (continued)

Carcinomas										Ependymoblastoma	Melanomas		Sarcomas and undifferentiated tumors								
PRZh	Ca-1025	Carcinoma NK	Ca Guerin	Rhabdomyosarcoma MOP	Ovarian tumor (OYa)	Ca-C3H	Hepatoma 129	Alveolar liver cancer (RS1)	Walker 256		B16	Harding-Passey melanoma	Ehrlich's ascites tumor	Ascites tumor NK/Ly	Sarcoma 37	Sarcoma 180	Sarcoma 536	Sarcoma AK	Sarcoma 45	Sarcoma M-1	Jensen's sarcoma
											+										
											++										
											−				−	−					
											++					+++					
											+++				++						
										+++	+					++					
−						++	+++			−	+++		++		+++	++					
										+	+				+++						
										+++	++										
−						++				−	++				++						
											−				++	+					
+++								++	++	+	+++		−			−	+		++	+	+++
−	+++					+				++	++				+++	+++					
										−	++				++	−					
															−	++					
										−	−					−					
										−	++				−	−					
											+		+++		+			+	+++	+	
			+++	+++	++				+++	−	++		+++	+++	+++	−			+++		
			+++							+	+					+++			+++	++	+++
−											−				+++	++					
						++			+++				+++	++	++	++			+++		
++										++	++					+++					
−											+++				+	−					
										+++	++										
−											+				−	−					
										+++	+++										
			+						+++		+	+							++		
											++				++	−					
										−	++										
						−				++	+++				+	++					
						+					−				+	−					
										−	−										
+											++										
											+				−	−					

tumor growth by 75–90%; +++ = ILS by ≧100% or inhibition of tumor growth by ≧90%.

TABLE 6.—*ILS of animals treated with drugs* [a]

Drug	L1210	P388	La	L-AK	MOPC-406	Ca-755	Lewis lung	AKATOL	RShM-5	Ca-C3H	PRZh	B16	Ependymoblastoma	S37	S180
Methotrexate	+++	+++	−		+	+	−	+	−		−	−		−	−
Tomizin	−	−	−				−	−				+++	−		
Quinoline derivative	+++	+++	+++			−	−	++	−			−			
5-FU	++	+++	+++		+++	−	+	+	−		−	++	+	−	−
Ftorafur	++	+	++		+	−	−	−	+			+	−	−	
3-Deazauridine	+	−	−			−	−		−			−			
Ara-C	+++	+++	−		−	−	−	−	+		−	+		−	−
Cyclocytidine	+++	+++	+		−	−	−	−	+			−	−	−	
5-Azacytidine	+++	+++	++	+	++	+	+	−	−	+	−	+		−	
6-Mercapto-purine	++	+	−		++	++	−	+	−			−		−	−
6-Thioguanine	++	+	−		++	+	−	−	−		++	+		−	−
α-Deoxythio-guanosine	++	++	−	+		++	−	−	−			−			
6-Selenoguano-sine	+++	++	−			+	++	+	++			++			
Inosine diglycol-aldehyde	+++	+++	+++	+++	+	−	−	−	−			−	−	−	−
Townsend's nucleoside derivative	+++	−	−			−	−	−	−			−			
DTIC	+	+	−		−	−	−	−	−		−	+		−	
Reumycin	−	−					−					−			
Hydroxyurea	+++	−	+++		+	−	−	+	−			+		−	−
Guanazole	+++	+	+++	+++	+	−	++	+	−	+	−	−	+	−	−
ICRF-187	+++	++	−			++	++	−	−		+	++	+		
Dactinomycin	+	+++	+++		+	−	−	−	−		−	++		−	−
Adriamycin	++	+++	+++		++	+	−	−	−		−	+++		−	−
Carminomycin	++	++	+++		+	−	−	−	−		−	+		−	
Olivomycin	++	+++	++			−	−					+			
Variamycin	−	++	++				−					+			
Aton	−	−					−					−	−		
Vincristine	+	+++	++		−	−	−	+	−		−	++			
Colchizin	−	+++	+++		+	−	−	−	−			+		−	−
Chanerol	−	−	−			+	−	−	−			−			
Glucomannan	−	−										−			
Agavoside	−	−				−	−					−	−		
Digitonin	−	−	+++				−					−	−		
Funkioside	−	−	++				−	−				−			
Vitalboside	−	−	+++				−					−			
Coralyne sulfoacetate	++	++					++					+			
Ellipticine	+++	+++		+			−					−	−		
Dichlorallyl lawsone	−	++					−					+			
Indicine-*N*-oxide	+	+++					−					++			
Nitrogen mustard	+	+++	+		++	−	−	−	−			++		−	−
Nordopan	++	+++	+++			−	+	−	+			++			

TABLE 6.—*ILS of animals treated with drugs*[a] *(continued)*

Drug	L1210	P388	La	L-AK	MOPC-406	Ca-755	Lewis lung	AKATOL	RShM-5	Ca-C3H	PRZh	B16	Ependymoblastoma	S37	S180
Dopan	++	+++	++		++	−	+	−	−			+			
Fluorodopan	+	++	−		−	+	−	−	−			+	+++		
Sarcolysin	+++	+++	+++	−+	+++	++	++	−	+	++	−	+++	−	++	+
Asaley	++	++	++		+	−	+	−				+	+	+	
Spirohydantoin mustard	++	+++	++			+	+		−			++	+++		
TIC-mustard	+++	+++	+	++	−	−	+	−	−	++	−	++	−	−	
Palphicerin	+	+++	−		+	+	−	−	−			++		−	−
Prospidine	−	+	−			+	++	−			+++	+++	+		−
Cyclophosphamide	+++	+++	+++	+++	+++	++	+++	+	++	+	−	++	++		+
Phenthyrine	−	++	−		−	+	+	−	+			++	−	−	
Estracyt	−		−			−	−		−					−	+
Phenestrol	−	−	−			−	−		−			−	−		
Distron	+	++	−		−	+	−	+	−			−	−	−	
Fotrin	++	−++	+++				−					+++		−	−
Dioxadet	+++	−++					−					++	−		
Diiodobenzotepa	++	+++					−					++	+		
Hexamethylmelamine	+	−	+		−	−	−	−	−			−		−	−
MNU	+++	+++	+			−			−						
BCNU	+++	+++	−	+		−	+++	−	++			++	++		
CCNU	+++	+++	−	+	−	+	++	−	−		−	+++		−	−
PCNU	+++	+++	−			++	−+	+	−			++	+++		
Streptozotocin	+	++	+++		+	−	−	+	−	+++	−	+			
Chlorozotocin	+++	+−+	−			+	+	−	++			+	+++		
Diazan	+	++	+++				−					+			
Myleran	−	−	−		−	−	−	−				−			−
Cain's acridine derivative	++	+++	−			−	+	−	++			++			
cis-Pt(II)	++	+++	+++	++	−	−	+	−	−	−		++	++		
Gallium nitrate	−	+	+++	−	−	−	−	−	−	+		−		−	−
S-Trityl-L-cysteine	++	+++		+			−					−	−		
Prednisolone (prednisone)	−	−	−			+	−	−	−			−			
Procarbazine	++	++	−		−	−	−	++	−			−		−	−

[a] *See* table 5 legend for definitions of symbols.

for maximum manifestation of effect. As a result, the antitumor activity of these drugs was higher at times when tested at the OSC and at others it was higher at the NCI. However, no fundamental discrepancy was observed in the evaluation of the presence of antitumor activity for the drugs in either place, despite the difference in the treatment schedules followed.

Indexes of Therapeutic Efficacy

For the same decision to be reached regarding the activity of a drug, observations with the identical therapeutic schedule may not necessarily be as important as the choice of index of effect in the evaluation. The primary criterion of effect of drugs on a tumor in the NCI has been the ILS of the treated animals as compared with controls. Also taken into account is the percent of cured animals. Growth inhibition of the tumor has not been used as extensively (*251, 252*).

At the OSC, the antitumor activity is evaluated on the basis of the duration of life and the percent of cured animals as well as the inhibition of growth of solid tumors at various times of observation (*253, 254*). Broad use is

TABLE 7.—*Effect of drugs on patients with tumors* [a]

Drug	Colon	Melanoma	Lung (small cell)	Breast	Ovary	Cervix	Prostate	Choriocarcinoma	Pancreas	Larynx	Stomach	Kidney	Wilms' tumor	Head and neck	Brain	Bladder	Neuroblastoma	Retinoblastoma	Myeloma	Sarcoma	Testes	Leukoses	Lymphomas
Methotrexate	⊕	−	+	+	⊕	⊕		+						+	⊕					+	+	+	+
Tomizin																							
Quinoline derivative																							
5-FU	+	−	−	+	+	⊕	⊕		+		+			+		⊕							
Ftorafur	+			+	+						+				⊕								
3-Deazauridine																							
Ara-C	−	−	−	−																		+	+
Cyclocytidine																						+	
5-Azacytidine	−			−																			
6-Mercaptopurine	−		−	−				⊕						⊕								+	
6-Thioguanine	−																					+	
α-Deoxythioguanosine																							
6-Selenoguanosine																							
Inosine diglycolaldehyde																							
Townsend's nucleoside derivative																							
DTIC	−	+	−	−													⊕			+			
Reumycin		⊕																					
Hydroxyurea	−	⊕	⊕	−								⊕		⊕								⊕	
Guanazole																							
Dactinomycin	−	⊕						+					+							+	+	⊕	+
Adriamycin	−	−	+	+	+	⊕	+		⊕		+		+	⊕		+	+		+	+	+	+	+
Carminomycin				+	⊕															+		⊕	+
Olivomycin		⊕	−		⊕			+												⊕			
Variamycin																							
Aton																							
Vincristine	−	−	⊕	+	−	⊕							+		⊕		+			+		+	+
Colchizin																							
Chanerol																							
Glucomannan																							
Agavoside																							
Funkioside																							

TABLE 7.—Effect of drugs on patients with tumors [a] *(continued)*

Drug	Colon	Melanoma	Lung (small cell)	Breast	Ovary	Cervix	Prostate	Choriocarcinoma	Pancreas	Larynx	Stomach	Kidney	Wilms' tumor	Head and neck	Brain	Bladder	Neuroblastoma	Retinoblastoma	Myeloma	Sarcoma	Testes	Leukoses	Lymphomas
Vitalboside																							
Coralyne sulfoacetate																							
Ellipticine																							
Dichloroallyl lawsone																							
Indicine-*N*-oxide																							
Nitrogen mustard	–	–	+	⊕	+		⊕				⊕											⊕	+
Nordopan																							
Dopan																						⊕	+
Fluorodopan																							+
Sarcolysin	–	⊕	–	+	+	⊕													+	⊕	+		+
Asaley	–		–	+																			+
Spirohydantoin mustard																							
TIC-mustard	–														⊕								
Palphicerin																							
Prospidine		⊕	–	⊕	+					+								+		⊕			+
Cyclophosphamide	⊕	⊕	+	+	+	+	⊕						+	+		⊕	+	+	+	+	+	+	+
Phenthyrine			–																			+	+
Estracyt							+																
Phenestrol																							
Distron																							
Fotrin																						+	+
Dioxadet			⊕	⊕	+																		
Diiodobenzotepa				+												+							
Hexamethylmelamine	⊕	–	⊕	⊕	+	⊕								⊕		⊕							+
MNU		+	+																				+
BCNU	⊕	⊕	⊕	⊕							⊕				+				+				+
CCNU	⊕	⊕	⊕	⊕	⊕										+								+
PCNU																							
Streptozotocin	–			–					+														⊕
Chlorozotocin																							
Diazan		⊕	⊕																				
Myleran			–				–															+	

TABLE 7. — *Effect of drugs on patients with tumors* (continued)*

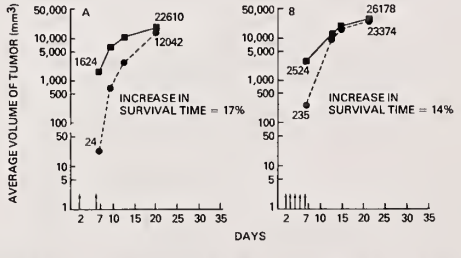
Drug	Colon	Melanoma	Lung (small cell)	Breast	Ovary	Cervix	Prostate	Choriocarcinoma	Pancreas	Larynx	Stomach	Kidney	Wilms' tumor	Head and neck	Brain	Bladder	Neuroblastoma	Retinoblastoma	Myeloma	Sarcoma	Testes	Leukoses	Lymphomas
Cain's acridine derivative																							
cis-Pt(II)	−				+	+								+		+				⊕	+		
Gallium nitrate																							
Procarbazine	−	−	⊕												⊕							+	+
Chlorambucil	−	−		⊕	+	⊕		+						⊕					+	⊕	+	+	+
Vinblastine	−	−	−	⊕				+						+	⊕		+				+		+
Mithramycin		−	−	−			−								⊕					−	+		
Daunorubicin																	+					+	⊕
Bleomycin	−	−	⊕	−		+				⊕				+							+		+
Mitomycin C	⊕	−	⊕	⊕		⊕			⊕		+					⊕							
Me-CCNU	+	+	⊕	−	−	⊕					⊕	−		⊕	+					−			
Dibromodulcitol	−	⊕	⊕	⊕								⊕		⊕									
L-Asparaginase																						+	
Dibromomannitol																						+	
Thio-TEPA				+	+											⊕							+

* Minus sign = inactive; plus sign = adequate evaluation and drug is active; encircled plus sign = evidence of drug activity but it is not clearly established.

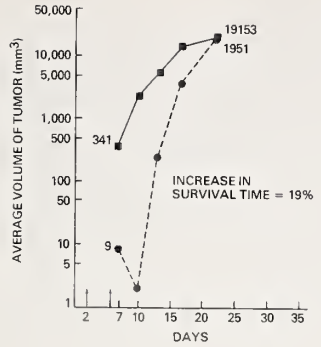
made of the kinetic indexes of tumor growth for evaluation of effect at the Institute of Chemical Physics of the USSR Academy of Sciences (*147*).

It is evident from the data presented here that when the antitumor activity of the drugs is determined according to different indexes (e.g., by the ILS or by the inhibition of tumor growth), the evaluation of the efficacy of therapy with some drugs may be different with regard to solid tumors. Thus in the testing of a large number of drugs against LL, some were considered inactive according to NCI's system but active according to that of the OSC (methotrexate, ftorafur, ara-C, cyclocytidine, vincristine, chanerol, glucomannan, agavoside, funkioside, vitalboside, fluorodopan, and others). The difference in the evaluation is related to the fact that, whereas these drugs cause a significant though temporary suppression of the growth of LL, they do not increase the life-span of the animals (text-fig. 1). A similar situation is observed in the study of the effect of hydroxyurea, guanazole, 5-FU, hexamethylmelamine, and gallium nitrate on the growth of Ca-755. These drugs cause marked inhibition of tumor growth but fail to prolong the lives of the treated mice (text-fig. 2).

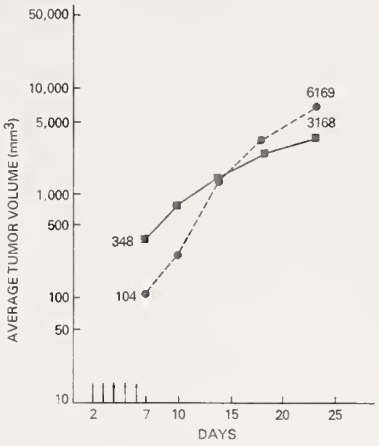
Use of similar drugs may also result in a temporary effect in the treatment of some solid tumors of man. For example, 5-FU has been observed to cause a pronounced immediate antitumor effect in the treatment of gastrointestinal cancer (*248, 255–257*). However, the treated patients do not necessarily live longer than those untreated. Despite a lack of clear evidence of an effect by 5-FU on life-spans of many patients with generally refractory solid tumors when used alone, the drug is nevertheless an established and valuable therapeutic agent and is



TEXT-FIGURE 1.—Dynamics of growth of LL after treatment with A) 300 mg ftorafur/kg, days 2 and 6, and B) 25 mg ara-C/kg, days 2–6. *Solid line* = control group; *dashed line* = experimental group.



TEXT-FIGURE 2.—Growth dynamics of Ca-755 after treatment with 50 mg 5-FU/kg on days 2 and 6. *See* text-figure 1 legend for line explanations.



TEXT-FIGURE 4.—Growth dynamics of S37 after treatment with 50 mg gallium nitrate/kg on days 2–6. Survival time for controls = 61 days; experimental animals = 43 days. *See* text-figure 1 legend for line explanations.

widely administered in the treatment of various human tumors, including gastrointestinal tumors.

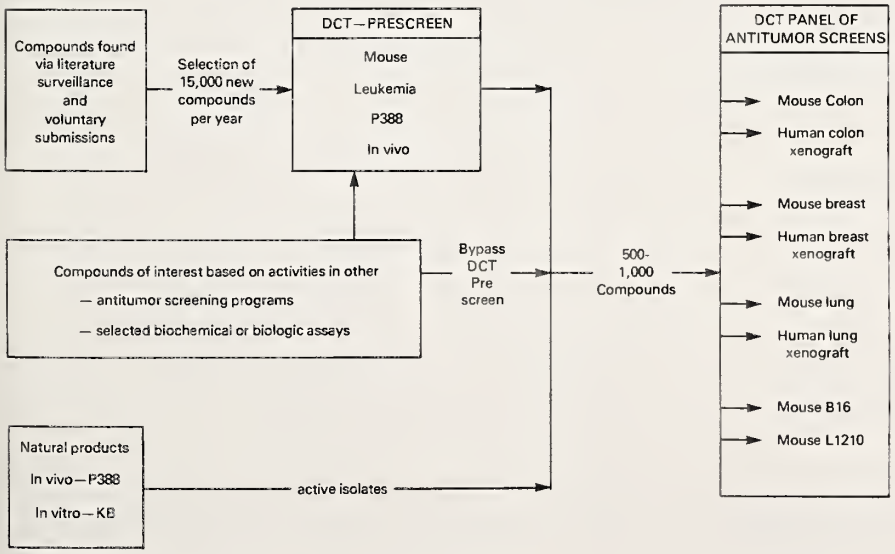
The same may be said of a number of other drugs practically applied in oncology. These substances are often used in combined therapy and thereby substantially increase the efficacy of treatment. Consequently, when rating a substance as active in the initial screening for new antitumor agents, scientists should give some consideration to reducing the extent of inhibition of tumor growth required for a drug to pass, so as not to miss potentially active substances. This is easily and conveniently done by measurement of the effect of drugs on tumor growth in animals with solid tumors. This type of rationale also served as a basis for the selection of leukemia P388 as a prescreen in the newly instituted screening program at the Division of Cancer Treatment, NCI, since its sensitivity to therapy may increase the number of compounds rated as active. A schema of the new screening program at the NCI that involves a panel of tumors (including human tumors growing in athymic mice) is shown in text-figure 3.

A special study conducted at the OSC by Z. P. Sof'ina suggested that, based on the pattern of activity in animal tumor systems, the existing drugs could be classified into 3 groups:

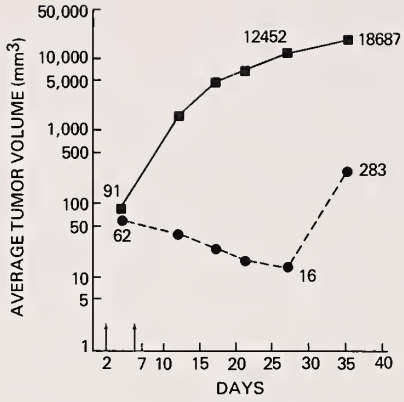
1) Some compounds only have an immediate, temporary antitumor effect. Of the drugs included in the study and under the prescribed experimental conditions, such an effect was observed with colchizin, gallium nitrate, Townsend's nucleoside derivative, the quinolinium derivative, and some others. These drugs usually did not increase the life-spans of animals with solid tumors and sometimes caused stimulation of neoplastic growth after pronounced inhibition (text-fig. 4).

2) The second group of drugs, which had a prolonged or delayed antitumor effect, included, e.g., cyclophosphamide, chlorozotocin, prospidine, palphicerin, phenestrol, 6-mercaptopurine, 6-thioguanine, α-deoxythioguanosine (text-figs. 5–7).

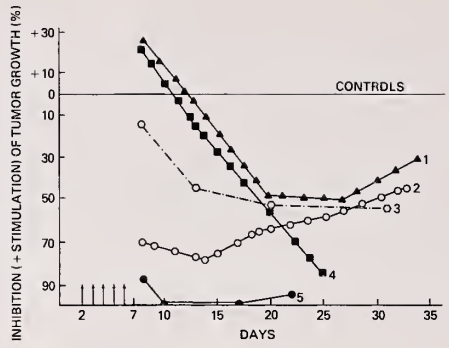
3) Antitumor agents in the third group included drugs that depended substantially on the growth rate of the



TEXT-FIGURE 3.—The Division of Cancer Treatment, NCI: Flow of drugs through screens.



TEXT-FIGURE 5.—Growth dynamics of AKATOL after treatment with 100 mg cyclophosphamide on days 2 and 6. *See* text-figure 1 legend for line explanations.



TEXT-FIGURE 7.—Growth inhibition of tumors by 6-thioguanine; 1) PRZh, 2) AKATOL, 3) RShM-5, 4) S37, and 5) Ca-755.

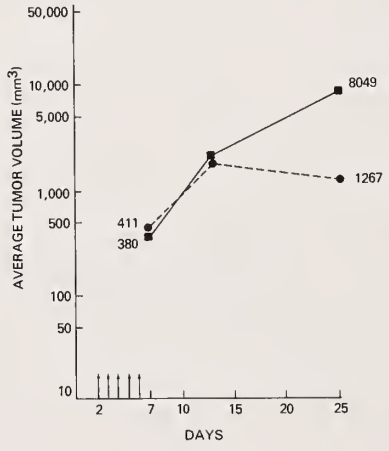
neoplasm for their rapidity of manifestation of effect and duration of suppressive action on tumor development (text-fig. 8): antimetabolites (e.g., ara-C, DTIC, 5-FU, ftorafur, guanazole, 3-deazauridine), some alkylating agents (sarcolysin, TIC-mustard, asaley, hexamethylmelamine, phenthyrine, etc.), and substances of natural origin (streptozotocin, vincristine).

The characterization of the effects of drugs is traceable to their mechanism of action, e.g., the temporary blocking effect of colchicine on cell division is well-known. Atwell and Cain (*85*) and Sof'ina et al. (*258*) have elucidated how quickly the blocking of methionine synthetase by the quinolinium derivative ceases after discontinuance of therapy.

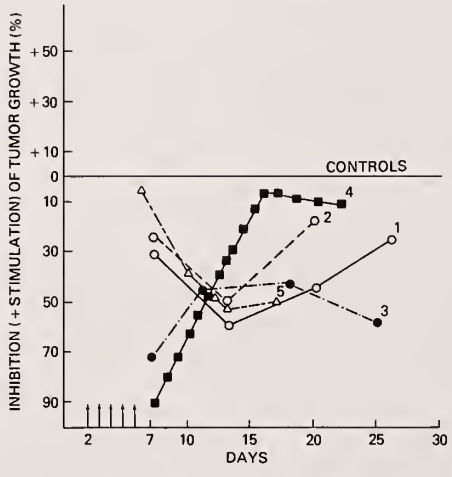
Townsend's nucleoside derivative causes a temporary block of purine nucleoside synthesis (*80, 81*). Thus compounds of the first group which cause a temporary block of the syntheses of various vitally important products would generally appear to exert a brief suppressive effect on tumor growth. The combination of this mechanism of action and the pharmacokinetic characteristics of the drugs (rapid elimination from the body or high rate of inactivation of the drug) leads to the possibility of rapid restoration of the damage inflicted and consequently to regeneration of the tumor.

Substances of the second group, with prolonged or delayed effects, include drugs that cause structural damage in DNA. This may occur not only as a result of alkylation of DNA but also as a result of incorporation of anomalous nucleotides. Both events lead to informational incapacity of the DNA. The latter may be manifested in two or three generations of cells, such as in the thiopurines (*129, 259, 260*). Of the alkylating agents, the drugs that require activation in the body [phenestrol (*134*); cyclophosphamide (*261*); prospidine (*262*)] belong to this category. The pharmacokinetic features of these compounds may also promote their prolonged action on the tumor.

The third group of drugs includes the antimetabolites which act on various stages of nucleic acid synthesis. Some drugs, such as 5-FU, have different points of attack when acting on cells of different metabolic types and cause irreversible changes in RNA function in some of them and reversible changes in metabolic levels in others



TEXT-FIGURE 6.—Growth dynamics of S37 after treatment with 1 mg 6-thioguanine/kg on days 2–6. *See* text-figure 1 legend for line designations.



TEXT-FIGURE 8.—Growth inhibition of various tumors by ara-C. 1) AKATOL, 2) S37, 3) RShM-5, 4) LL, 5) Ca-755.

(*263, 264*). Also included are some alkylating agents which are rapidly inactivated or eliminated from the body and the intercalating agents, dactinomycin and anthracycline antibiotics (*162*). The effects of these drugs are exerted to the greatest degree on dividing cells. However, under conditions of active proliferation, the process of regeneration of damage inflicted by these substances may also be facilitated. As a result, the well-known dependence of effect on the proliferative activity of the tumor cells is especially characteristic of this group (*265–268*).

Clinical experience has indicated that the above-listed properties of the drugs may also be manifested when they are administered to the patient with cancer. Mention was made above of the brief effect 5-FU may have on tumors of the gastrointestinal tract in man. Also, several authors have reported on the prolonged duration of the effect of cyclophosphamide, prospidine (*262*), and *cis*-Pt(II) (*269, 270*) in the treatment of solid tumors. A large series of clinical investigations devoted to optimization of the application of cycle- and phase-specific substances also suggests that the dependence of drug effect on the growth rate of the tumors is important in clinical practice (*269, 271–273*).

Thus, the information obtained by experimental study of the dynamics of the changes in tumors under the influence of antitumor drugs is significant, inasmuch as it may contribute to prediction of these characteristics in the treatment of the patient.

Dependence of Effect on Dose and Other Factors

Because dose–response studies make important contributions to the information obtained, it is highly desirable to perform them for evaluation of drug effects. Evaluation is invariably done in testing at the NCI, but, unfortunately, dose–response studies are not always conducted by other investigators in the United States and in the Soviet Union.

Establishment of dose–response curves makes possible the determination of the effect of the optimal dose on the tumor. A number of factors may influence the sensitivity of animals to antitumor agents: Different strains of animals react differently to the same drug as do animals bearing different tumors. For example, because CBA mice are 2.5 times more susceptible to *cis-Pt* (II) than mice of other strains, it is necessary to reduce the dose of the drug when treating them from 2.5 mg/kg, which is usually well tolerated by mice of other strains, to 1 mg/kg.

Sex differences also exist in the susceptibility of animals to some drugs (*274–277*). For example, the LD50 of asaley for female rats is 450 mg/kg and for males 235 mg/kg. The LD50 doses of sarcolysin are 19 and 14 mg/kg, respectively, for female and male rats (*278*).

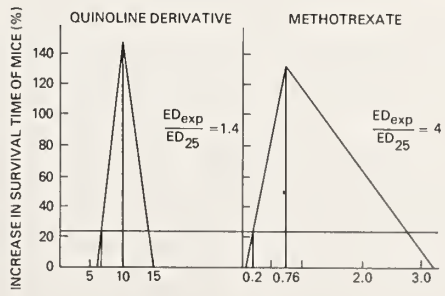
Seasonal and circadian fluctuations in susceptibility of animals to antitumor compounds also occur. Significant seasonal fluctuations have been observed in the susceptibility of mice to cyclophosphamide, 5-FU, and olivomycin (*279–281*). The same dose of cyclophosphamide (450 mg/kg) caused the death of 20% of the animals in March and 90% in August. Injection of 5-FU (240 mg/kg) during the winter was less toxic (caused death in 25% of the animals) than in summer (70%). The circadian fluctuations in the toxicity of olivomycin were extensive (90% of the mice died from a dose of 8 mg/kg given at 11:00 a.m. and 20% when the same dose was given at 8:00 p.m.); with 5-FU, 90% died when a dose of 240 mg/kg was given at 8:00 a.m. and 30% at 8:00 p.m.; 75% of the mice died from a dose of 22 mg sarcolysin/kg given at 8:00 a.m. and none died when the drug was injected between 2:00 and 5:00 p.m.

Similar to the above observations are the variations that occur among experiments in the optimal doses of different drugs. Thus it may be noted that the optimal dose of cyclophosphamide when given once to mice on the 5th day after the inoculation of L1210 ranged from 140 to 300 mg/kg (Appendix I). When mice with LL were treated with 5-FU, the optimal dose in 1 experiment was 20 mg/kg, and in another it was one-half as much. The optimal doses of olivomycin also varied by a factor of 2–4.

Sensitivity of tumors to chemotherapeutic agents also has seasonal and daily fluctuations, but they may be less pronounced than in that of normal tissues. These differences in the behavior of normal tissues and tumors can conceivably be used to increase the selectivity of action against the tumors. For this reason it would clearly be advantageous to inject drugs at the moment normal tissues are least susceptible (*280, 282–284*).

The optimal dose of a drug may vary even when the experiments are conducted under specified conditions. Ascertainment of optimal doses requires constant use of a series of doses of the drugs being studied in each experiment.

Dose–response experiments make it possible for one to determine not only the therapeutic effectiveness of drugs but also the range of safe effective doses (therapeutic or specificity index). The therapeutic index (or specificity index) of drugs for a tumor is usually defined as the ratio of the dose causing a specified degree of toxic effect for the host relative to the dose eliciting a defined therapeutic effect. An example of a broad and a narrow specificity index is presented in text-figure 9. Methotrexate has a broad range of effective doses in the treatment of L1210. If a 25% increase in life-span of the treated mice (ED25) is designated as the minimum criterion of therapeutic effect, then the optimal dose (ED_{opt}) of methotrexate by



TEXT-FIGURE 9.—Dependence of antitumor effect of quinoline derivative and methotrexate on dose, according to data of Skipper and Schmidt (*285*) and Sof'ina (unpublished).

daily injection in mice with L1210 is four times higher than the minimally active dose, i.e., about 0.8 and 0.2 mg/kg (*285*). An example of a drug that evidenced a narrower range of effective doses, but against a different tumor, is Cain's quinoline derivative (Sof'ina ZP: Unpublished data). The ratio of optimal dose of this drug to the dose giving a 25% increase in survival time in the treatment of La is about 1.4:1 (text-fig. 9).

The range of effective doses may be different even for the same drug in the treatment of different tumors. For a tumor that is more susceptible to a drug, one can expect the range of effective doses to be greater.

Thus analysis of the systems for studying antitumor drugs in the United States and the Soviet Union has emphasized that:

1) In the screening of new drugs, attention should be given to the criteria of therapeutic efficacy. Evaluation of the antitumor effect according to several parameters is desirable.

2) The effect of the drugs on different tumors should be determined on the basis of establishment of dose–response curves. This permits comparison of response at optimal doses or fractions thereof and comparison of the shapes of the curves, permitting determination of the margin of safety (therapeutic index or specificity index) with which the drugs can be used.

3) It is highly important in the establishment of the maximum therapeutic effectiveness of drugs that they be examined on different schedules of administration.

B: RATIONAL SELECTION OF EXPERIMENTAL MODELS FOR STUDYING ANTITUMOR DRUGS

Susceptibility of Experimental Models to Antitumor Drugs

Experience in chemotherapy has shown that a definitive number of drugs evaluated in experimental systems as active also manifest some antitumor effects when they are used to treat human tumors. Nevertheless, not all substances found to exert antitumor activity in clinical testing are then proposed for widespread use. The lack of interest in the introduction of such compounds into general practice is frequently attributable to the consideration that the drugs do not have any definite advantages over those already available. Alternatively, the drugs may be shelved because of the undesirable toxicologic properties.

Each of the many experimental systems surely has some definite value. However, the abundance of experimental models compels a search for a rational approach to their selection. For this purpose, an analysis of the cooperatively obtained data was undertaken.

For a resolution of the question of the optimal assembly of experimental tumors for screening drugs, an evaluation of the importance of the information received from each system separately and from all the data for the entire series of models was necessary. In this respect, a primary question arose: Do tumors of the same type react in the same way (all leukemias, carcinomas, sarcomas, melanomas) to the same drugs? Analyses of the data showed that the susceptibility of an experimental tumor to a drug is not determined by its classification as a specific histologic type. Actually, as may be seen in table 5, the presence of an antitumor effect by a drug against a single line of leukemia, carcinoma, sarcoma, or melanoma does not mean that others of the same tumor lines will react to the drug in the same way. For example, methotrexate, ara-C, ICRF-187, various nitrosourea derivatives, and numerous other drugs strongly suppressed the growth of L1210, but the same drugs were not active against La. The reverse relationship was observed for variamycin, colchizin, digitonin, funkioside, vitalboside, and gallium nitrate.

The response of different carcinomas to the same antitumor drug may also be variable (table 5). A drug may totally suppress the growth of one carcinoma and not influence the growth of another at all, or there may be less dramatic differences in degree of effect. A drug may or may not suppress the growth of several carcinomas. Thus inosine diglycolaldehyde was not effective against any of the solid mouse tumors studied, but ellipticine and estracyt acted against three carcinomas. On the other hand, 6-selenoguanosine, hydroxyurea, carminomycin, chanerol, agavoside, funkioside, coralyne sulfoacetate, Nordopan, prospidine, distron, BCNU, PCNU, and Cain's acridine derivative manifested antitumor activity against all the carcinomas used. What the similarities and differences are in the properties of carcinomas that accounted for the above responses is not clear. Likewise, no definite pattern of response by all sarcomas to treatment with anticancer agents was observed.

Nevertheless, the reactions of some tumors to drugs differ little. For example, L1210 and P388 often differ only in the degree of susceptibility to the same drugs. Generally, more P388 is susceptible than L1210.

An analysis of the data indicates that each experimental tumor usually has its specific spectrum of sensitivity to antitumor drugs. Also, animal leukemias are more susceptible to chemotherapy than are solid tumors. This susceptibility is manifested in a considerably prolonged life-span of animals with leukemias than those with solid tumors after treatment with the various antitumor agents. A similar pattern has been observed clinically.

An examination of the data obtained focuses attention on the fact that each of the experimental neoplasms (both leukemias and solid tumors) react to substances of a specific type of mechanism of action. Results of the effect of drugs on the animals' life-spans are pertinent in this regard (table 6).

Thus L1210, which has a broad spectrum of sensitivity to antitumor agents, reacted strongly to antimetabolites of nucleic acid metabolism (analogs of pyrimidines, purines, folic acid, and ribonucleotide reductase inhibitors) and several alkylating substances, especially nitrosourea derivatives. Membrane-interacting substances and compounds, which intercalate into DNA, usually have reduced effect or none at all on this leukemia.

The susceptibility spectrum of La is different. This tumor, as opposed to L1210, does not react strongly to the purine analogs and nitrosourea derivatives, but it is highly susceptible to intercalators (antibiotics) and to mitotic poisons.

One can see in table 6 that Ca-755 is susceptible to purine analogs and to a number of alkylating substances (chlorethylamine and nitrosourea derivatives). LL is susceptible to ribonucleotide reductase inhibitors (guanazole) as well as to chlorethylamines and nitrosourea derivatives. The adenocarcinoma of the large intestine, AKATOL, is highly sensitive to analogs of folic acid, to some analogs of purines, and to ribonucleotide reductase inhibitors. Its reaction to chlorethylamines is weak and, in contrast to many experimental tumors, it is sensitive to procarbazine. Squamous cell uterine cervix cancer RShM-5 is of low susceptibility to most drugs except for pyrimidine analogs.

Research on the cytotoxic effect of drugs in suspension cell cultures of a number of animal tumors (table 8) has also indicated that their effect in these systems is related to their mechanism of action. Thus the analogs of pyrimidines and purines, as well as substances which intercalate into DNA, manifested the greatest cytotoxic effect against S37 cells. Ehrlich ascites tumor showed selective sensitivity to ribonucleotide reductase inhibitors. Membrane interacting substances displayed high activity against NK/Ly.

Some of the substances had cytotoxic action against all the in vitro systems used. These included adriamycin, carminomycin, BCNU, and dioxadet. Reduced cytotoxic effect was observed with 5-FU, nitrogen mustard, 6-selenoguanosine, agavoside, and vitalboside. A comparison of these data with the results of a study of the drugs in vivo and clinically suggests that substances with narrow spectra of cytotoxic effect in vitro generally also possess narrower ranges of effect against animal and human tumors and that drugs which suppress the reproduction of cells of all types of tumors considerably in vitro have broad spectra of antitumor action in vivo against animal and human tumors.

Clarification of the observed differences in sensitivty of tumors to various kinds of drugs requires, first of all, elucidation of their metabolic characteristics.

Factual material obtained in the present investigation can be interpreted from this point of view. Biochemical studies of the two murine leukemias La and L1210, which are similar in cell cycle parameters but differ strongly in susceptibility to drugs, have led to the conclusion that they also differ substantially in some metabolic characteristics. For instance, the moderate susceptibility of the L1210 cells to 5-FU could be explained by the observation that the cytotoxic effect of this compound against leukemia cells is attributable to inhibition of the synthesis of thymidylate de novo and that this metabolic block is partially alleviated by a significant salvage pathway of thymidylate synthesis. The higher susceptibility to 5-FU of La cells may be caused by a double blockade. For this tumor, the drug not only suppresses thymidylate synthetase but also, by competing successfully with the natural substrate uridine 5′-triphosphate for RNA polymerase, is incorporated into RNA and interferes with its function. In addition, in La cells the rate of thymidylate synthesis de novo significantly exceeds the capacity of the salvage pathway. Hence, the latter pathway cannot fully compensate for the blocking of thymidylate synthetase by 5-FU (*263*).

For the analogs of cytidine, ara-C, and 5-azacytidine, an opposite pattern prevails. La is far less susceptible to these drugs than is L1210. In an analysis of the nucleotide pool of these leukemias, attention is focused on the extremely low level of cytidine nucleotides in L1210 cells. Perhaps this deficit in cytidine derivatives may serve as a basis for the higher susceptibility of L1210 cells to ara-C and 5-azacytidine (*263*).

Leukemias L1210 and La differ also in metabolism of purine nucleotides, and this may account for their differences in susceptibility to purine analogs (*264*).

Because 6-mercaptopurine and 6-thioguanine perform a double blockade of the biosynthesis of purine nucleotides de novo, it is generally considered that the susceptibility of the cells of various tumors to these drugs should depend on the potential capacity of this de novo pathway and its contribution to the total metabolism of purine nucleotides. In Ca-755, which is highly susceptible to 6-thiopurines, the synthesis of purines de novo exceeds the salvage pathway twofold; the same relationship also exists in Ehrlich ascites tumor. However, for La, which is only slightly sensitive to 6-thiopurines, the de novo pathway is four to six times in excess of the salvage pathway. Consequently, the ratio of the rates of synthesis of purines de novo and that of the salvage pathway may not always serve as an index of the susceptibility of the tumor to purine analogs.

One of the criteria of susceptibility of tumor cells to 6-thiopurines is the activity of the enzyme HGPRT involved in lethal synthesis to the active mononucleotides. Whereas L1210 is moderately sensitive to 6-thiopurines, La hardly reacts to them, and, correspondingly, the activity of HGPRT in L1210 cells is four times higher than in La cells (*264*).

The cause of the delayed death of tumor cells as a result of 6-mercaptopurine and 6-thioguanine action is their incorporation into the DNA and RNA molecules with subsequent interference with their functions. During the development of resistance by L1210 to 6-mercaptopurine, the ability of the analog to be incorporated into nucleic acids decreases sharply compared with the initial sensitive strain (*264*).

The cause of the high susceptibility of La to antibiotics is not clear, although it is known that their cytotoxic effect is based on their capacity to intercalate into DNA and to disturb the process of transcription.

That data on the spectrum of sensitivity of tumors to drugs with specific mechanisms of action can provide important information on characteristic features of their metabolism must be emphasized. Thus the high sensitivity of L1210 and La, Ca-755, and Ehrlich carcinoma to ribonucleotide reductase inhibitors indicates that this enzyme plays an important role in the synthesis of deoxyribonucleotides in these tumors, whereas transglycosidase reactions are not as important. The higher susceptibility of AKATOL adenocarcinoma to 6-thioguanine compared with α-deoxythioguanosine and 6-selenoguanosine points to the high activity of lethal synthesis by HGPRT and the low activity of the transglycosidases and kinases in

TABLE 8.—*Some characteristics of*

Drug	Solubility	Total dose, mg/kg	Optimal therapy schedule			Type of action			Effect, Blocking of				
			Daily	Intermittent, 8 times/day	Intermittent, once/day	Immediate effect	Delayed effect	Effect depends on tumor growth rate	Purines	Pyrimidines	Thymidylate	Ribonucleotide reductase	Folic acid cycle
Methotrexate	W	20			+			+	+		+		+
Tomizin	W	350–750	+			+			+		+		+
Quinoline derivative	NA	25–40	+			+			+		+		+
5-FU	W	100–200			+			+			+		
Ftorafur	W	500–1,500			+			+			+		
3-Deazauridine	W	1,500	+					+		+			
Ara-C	W	125–150		+				+		+		+	
Cyclocytidine	W	600–800			+			+		+		+	
5-Azacytidine	W	12–16			+		+			+			
6-Mercaptopurine	W	150–200	+				+						
6-Thioguanine	W	5	+				+						
α-Deoxythioguanosine	NA	500	+				+		+				
6-Selenoguanosine	NA	125–150	+				+		+				
Inosine diglycolaldehyde	W	500–600			+				+			+	
Townsend's nucleoside derivative	NA	75–100	+			+			+				
DTIC	W	350–400			+			+					
Reumycin	W	7–15	+										
Hydroxyurea	W	2,500		+				+					
Guanazole	W	5,000		+				+				+	
ICRF-187	W	1,500			+		+					+	
Dactinomycin	NA	0.6			+	+							
Adriamycin	W	7.5–8			+								
Carminomycin	W	1–5			+	+							
Olivomycin	W	20–25			+								
Variamycin	W	1.25–4	+										
Aton	NA	500	+										
Vincristine	W	1.2			+	+		+					
Colchizin	W	340–600	+			+							
Chanerol	W	50–80	+			+		+					
Glucomannan	W	1,000–1,500	+										
Agavoside	W	25–35	+			+							
Digitonin	W	50–100	+			+							
Funkioside	NA	35–100	+			+							
Vitalboside	NA	50–100	+			+							
Coralyne sulfoacetate	W	500–600			+	+							
Ellipticine	NA	1,000	+										
Dichlorallyl lawsone	NA	500	+										

the oncolgical effect of drugs [a]

parameter, and drug properties

Mechanism of action										In vitro ED50, μg/ml			
biosynthesis and enzymes					Type of interaction								
ATP	Active transport	DNA	RNA	Proteins	Nucleic acids	Membranes	Hormone receptors	Microtubules	Enzymes	S37	L-5178Y	Ehrlich ascites tumor	NK/Ly
	+	+	+							0.001 [b]	0.1–0.001	<0.001 [b]	0.1–001
		+	+							100IA	100 IA	100 IA	100 IA
		+	+							50–10 [b]	50–10 [b]	50–10 [b]	50–10
		+	+	+						<0.1 [b]	<0.1 [b]	<0.1 [b]	1
		+	+	+						<10 [b]	50–10	50–10	<10 [b]
		+	+							10	10	<10 [b]	10
		+	+	+						<1 [b]	<1 [b]	100–50	10–1
		+	+	+						<20 [b]	500–200	500 IA	500 IA
			+	+						0.1 [b]	10–1	1	10–1
										50–20 [b]	500	250–100	250–100
										<20 [b]	100–50	<20 [b]	50–20
		+								100 IA	100 IA	100 IA	100 IA
			+							100–50	50–10 [b]	50–10 [b]	50–10 [b]
		+	+							100–75 [b]	75 [b]	250–100	100–75
		+	+							<10 [b]	<10 [b]	<10 [b]	<10 [b]
		+	+	+	a	a				500–250	500–250	500 IA	500 IA
+			+							100 IA	100 IA		10 [b]
										500	500	<50 [b]	200 IA
		+								2,000 IA	2,500	250–100 [b]	2,000
		+								100 IA	100 IA	500 IA	100 IA
		+	+	+	i					0.001–0.0001	0.001–0.0001 [b]	<0.001	0.01–0.001
		+	+	+	i					<1 [b]	<1 [b]	<1 [b]	<1 [b]
		+	+	+	i					<0.1 [b]	<0.1 [b]	<0.1 [b]	<0.1 [b]
			+	+	i					<0.1 [b]	1–0.1	1–0.1	1–0.1
			+	+	i								
										10–1	1–0.1	0.1 [b]	1–0.1
									c	100–50	20 [b]	50	100–50
									c	50–20	<10 [b]	50–20	100–50
										50–20 [b]	50–20 [b]	100–50	<50
+	+					c				50–10 [b]	50–10 [b]	50–10 [b]	50–10 [b]
+	+					c				100–50	100–50	100–50	50–10 [b]
+	+					c				50–10	<10 [b]	50–10	<10 [b]
+	+					c				50–10 [b]	50–10 [b]	50–10 [b]	50–10 [b]
			+							100 IA	100 IA	100 IA	100 IA
										Poorly soluble			

TABLE 8.—*Some characteristics of the*

Drug	Solubility	Total dose, mg/kg	Optimal therapy schedule			Type of action			Effect, Blocking of				
			Daily	Intermittent, 8 times/day	Intermittent, once/day	Immediate effect	Delayed effect	Effect depends on tumor growth rate	Purines	Pyrimidines	Thymidylate	Ribonucleotide reductase	Folic acid cycle
Indicine-*N*-oxide	W	7,000	+				+						
Nitrogen mustard	W	0.5	+			+							
Nordopan	NA	2–2.5	+										
Dopan	NA	2–3	+										
Fluorodopan	NA	120			+			+					
Sarcolysin	W	14–20			+			+					
Asaley	NA	200			+			+					
Spirohydantoin mustard	NA	30–100	+			+							
TIC-mustard	NA	240–300	+					+					
Palphicerin	NA	125	+				+						
Prospidine	W	1,000	+				+						
Cyclophosphamide	W	200			+		+						
Phenthyrine	W	300–400	+			+							
Estracyt	W	500	+				+						
Phenestrol	NA	500–1,200	+				+						
Distron	NA	125–300	+				+						
Fotrin	W	180–240	+					+					
Dioxadet	W	10–20	+										
Diiodobenzotepa	NA	400–600	+										
Hexamethylmelamine	NA	750	+					+					
MNU	NA	120	+		+								
BCNU	NA	70–80			+		+						
CCNU	NA	50–60			+		+						
PCNU	NA	10–20			+		+						
Streptozotocin	W	250	+					+					
Chlorozotocin	W	25–38			+		+						
Diazan	W	20–100			+								
Myleran	NA	100	+										
Cain's acridine derivative	NA	50–100	+		+			+					
cis-Pt(II)	W	8			+		+						
Gallium nitrate	W	250	+			+							
S-Trityl-L-cysteine	W	1,250											
Prednisolone (prednisone)	NA	0.5	+				+						
Procarbazine	NA	625	+				+						

[a] W= preparation dissolves in water; NA = drug dissolves in nonaqueous solvents; the ED50 indicated in the table as two figures

[b] These systems have the greatest activity.

oncological effect of drugs[a] (continued)

parameter, and drug properties													
Mechanism of action										In vitro ED50, μg/ml			
biosynthesis and enzymes					Type of interaction								
ATP	Active transport	DNA	RNA	Proteins	Nucleic acids	Membranes	Hormone receptors	Microtubules	Enzymes	S37	L-5178Y	Ehrlich ascites tumor	NK/Ly
										500 IA	500 IA	500 IA	500 IA
										1–0.1 [b]	1–0.1 [b]	<1 [b]	1–0.1 [b]
	+	+	+	+	a					20–10	50–20	10 [b]	10 [b]
	+	+	+	+	a					<1 [b]	20–10	<1 [b]	1
		+	+		a					50	100–50	<50 [b]	<50 [b]
+		+	+	+	a					10–1	10–1	<1 [b]	<1 [b]
+		+			a	a				10 [b]	50–10	10 [b]	50–10
					a								
		+	+	+	a					50–20 [b]	100–50	100–50	100–50
+		+	+	+	a	a				100–50 [b]	100–50 [b]	100 IA	100 IA
		+	+		a					500 IA	500 IA	500 IA	500 IA
		+	+	+	a				a	"	"	"	"
		+	+	+	a					<50 [b]	<50 [b]	<50 [b]	<50 [b]
		+	+	+	a		a			Poorly soluble			
		+	+	+	a		a						
		+	+		a					500–250	500 IA	250–100 [b]	500 IA
		+	+		a					<10	<10	<10	<10
		+	+		a					Poorly soluble			
		+	+	+	a	a			a	100 IA	50–10 [b]	100 IA	100 IA
		+	+	+	a	a			a	10–1 [b]	10–1 [b]	10–1 [b]	10–1 [b]
		+	+	+	a					100	100	100–50 [b]	100–50 [b]
		+	+	+	a					<50 [b]	<50 [b]	<50 [b]	<50 [b]
+		+	+		a			a		500 IA	500 IA	500 IA	500 [b]
		+	+		a					>100	100 IA		100 [b]
										100–50 [b]	100 IA	100 IA	100 IA
										100 IA	100 IA	100 IA	100 IA
		+	+		c					<50	<10 [b]	<10 [b]	20–10
										100–50 [b]	100	250–100	100–50 [b]
										<50 [b]	250–100	500–250	500 IA
										100 IA	100 IA	100 IA	100 IA

means that the ED50 is in the interval between the concentrations listed. a = alkylation; i = intercalation; c = bound; IA = inactive.

TABLE 9.—*Percent antitumor effect of 6-thiopurine and 6-selenopurine on various experimental tumors* [a]

	Tumor											
	L1210	La	Ca-755			AKATOL			RShM-5			B16
Drug	ILS	ILS	1 d	7–8 d	ILS	1 d	7–8 d	ILS	1 d	7–8 d	ILS	ILS
6-Thioguanine	53	+8	87	99.8	40	95	95	21	14	68	0	31
α-Deoxythioguanosine	54	2	97	99	82	+22	64	14	2	+23	11	12
6-Selenoguanosine	63	17	97	99.4	48	66	66	40	55	66	53	51

[a] 1 d and 7–8 d = inhibition of tumor growth 1 day or 7–8 days after treatment.

this tumor (table 9). Conversely, RShM-5 is practically resistant to 6-thioguanine and moderately sensitive to 6-selenoguanosine. These reactions suggest that in RShM-5 cells, lethal synthesis of 6-thioguanine is not significant because of a low level of HGPRT, whereas adequate activity of purine nucleotide glycosidases permits the activation of 6-selenoguanosine. A similar relationship of these enzymes apparently also exists in melanoma B16.

Selection of Experimental Models for the Study of Antitumor Drugs

New analogs of known antitumor agents are often tested in tumor models which possess high sensitivity to that class of compound. However, an analysis of the data shows that such models are useful primarily in the investigation of special problems, but they may not be sufficiently discriminating for screening. For example, it is inadvisable for one to screen analogs in tumor systems that have high sensitivity to the specific class when the objective is to find analogs with different mechanisms of action and spectrums of activity. If the test system is extremely sensitive, it may be too difficult to detect more active analogs.

To illustrate this, we can cite a number of examples. Some chlorethylamine derivatives known to differ in their spectra of action against human tumors (*see* table 7) differ little in their effectiveness against sarcomas 298 and 45 and Walker carcinosarcoma 256, tumors that are highly susceptible to chlorethylamines. Alternatively, a difference in the action spectra of these drugs is clearly manifested when studies with them are conducted on tumors with different susceptibility spectra (table 10).

It also appears less useful to attempt to find a difference in the spectra of antitumor action of derivatives of nitrosoureas with L1210, LL, and AKATOL adenocarcinoma of the large intestine. The differences in drug response are significantly more manifest if La, Ca-755, and RShM-5 cancer of the uterine cervix are used (table 11). With the latter systems, a substantial difference in the effect of streptozotocin and some for MNU becomes apparent as in the therapy of patients. Streptozotocin differed most in its activity spectrum. On tumors highly susceptible to nitrosoureas, it was less effective.

Studies on Ca-755, which is highly susceptible to purine analogs, yielded no substantial information on the action spectra of these drugs. However, all the information obtained with L1210, LL, AKATOL, and RShM-5 revealed definitive differences among the drugs (table 12). The nature of these differences has already been elaborated in the foregoing section.

Therefore, practically no new information can be obtained from several models as compared with one model, if they are similar in susceptibility to drugs.

Where primary screening is being conducted with these models, we suggest that one of them be selected and then the system be supplemented with tumors differing in their susceptibility spectra. Of the two leukemias, L1210 and P388, only one need be chosen for initial testing. This is presently being done at the Division of Cancer Treatment, NCI, where P388 is the initial prescreen and then L1210 is used for further evaluation as part of a tumor spectrum.

The most valuable information on the antitumor properties of drugs is obtained with a system composed of models that are substantially dissimilar in their susceptibility spectra to drugs with different mechanisms of action. Such systems make possible the detection of alterations in mechanisms and in the spectrum of antitumor effect.

At the same time, a search may be conducted for drugs with the same spectrum of antitumor activity but with greater selectivity of antitumor action in systems with specific sensitivity to the given class of compounds. Com-

TABLE 10.—*Effect of chlorethylamine derivatives with different clinical antitumor activity spectra on experimental tumors* [a]

	Tumor							
Drug	S-298	S-45	Walker 256	L1210	La	Ca-755	AKATOL	RShM-5
Sarcolysin	+++	+++	+++	+++	+++	+++	+	+++
Dopan	++	++	+++	++	++	−	−	−
Phenthyrine	++	++	++	−	−	+++	−	+
Prospidine		++	++	−	−	++	++	+

[a] *See* table 5 for definitions of symbols.

TABLE 11.—*Antitumor activity spectra of nitrosourea derivatives* [a]

Drug	Tumor						
	L1210	LL	AKATOL	La	Ca-755	B16	RShM-5
BCNU	+++	+++	+++	−	++	++	+++
CCNU	+++	+++	++	−	+	+++	+
Chlorozotocin	+++	++	++	−	−	+++	+++
Streptozotocin	+	−	++	+++	−	+	+
MNU	+++	++	++	+	++		+

[a] *See* table 5 for definitions of symbols.

parison of parameters pertaining to damage to the tumor and normal tissues, expressed in appropriate indexes, may serve as the criterion of selectivity of their effect.

The Breadth of the Antitumor Spectrum and Specificity of Antitumor Effect of Drugs

Of particular interest is the problem of breadth of the spectrum of antitumor action. A comparison of experimental and clinical data for the drugs permits examination of this question.

Tables 5 and 7 show that, generally, drugs having a broad spectrum of antitumor activity in experimental systems also possess it in clinical therapy. Cyclophosphamide, methotrexate, 5-FU, adriamycin, nitrosourea derivatives (except streptozotocin), hexamethylmelamine, sarcolysin, *cis*-PT(II), among others, are characterized by broad spectra of antitumor activity. However, ara-C, cyclocytidine, inosine diglycolaldehyde, hormone cytostatics, myleran, DTIC, etc., have narrow spectra. Still other drugs occupy an intermediate position.

Evidently, compounds with broad spectra of activity vitally damage systems important for all tumors. Drugs with narrow spectra appear to exert an effect against systems vital for only individual types of tumors. Although broad-spectra compounds command a high degree of interest, others with a specific, directed action should also receive considerable attention. When the point of attack is sufficiently different from that which obtains in vital tissues of the host, such drugs should in principle act on tumors more selectively.

The results of theoretical studies in oncology indicate that the effect of drugs that exert action against specific metabolic targets in tumor cells can continue to do so, provided that the tumor cells retain their initial characteristics. However, progression of the tumor usually leads to loss of specific features that could serve as the basis for directed action of a therapeutic agent (*286, 287*). For instance, hormone and immunologic specificity may be lost. As a result, it is often true that a drug which initially controlled the growth of a tumor ceases to act against it as the disease progresses. Some tumors are not susceptible to the action of the known antitumor agents from the moment of their origin. Substances with activity related to enzymes or substrates present in some and absent in other tumors may also exert specific biochemical action; the classic example of such a drug is L-asparaginase.

Current knowledge of malignant growth does not yet permit the widespread use of approaches to the preparation of antitumor drugs with specific biochemical action for the treatment of most tumor types. In the meantime, drugs with broad spectra of antitumor action that do not possess strong specificity are being used successfully in oncologic therapy and, undoubtedly, will continue to occupy a significant position in the arsenal of chemotherapeutic agents.

Nevertheless, it is highly important that scientists continue to devise means for the elaboration of specifically active antitumor agents. Experience has shown that it is advisable for such drugs to be investigated in special test systems.

The characterization of drugs with potential hormone activity should include testing with hormone-susceptible tumors and with pertinent endocrinologic investigations. The activity of these substances may not be revealed in other test systems. An example is provided by the use of estrogen derivatives, such as estracyt and phenestrol (*134, 288, 289*). Table 13 presents data on the effect of phenestrol on estrogen-susceptible cancer of the mammary gland RMC-1, hormone-susceptible adenocarcinoma Ca-755, and tumors that manifest predominant susceptibility to

TABLE 12.—*Antitumor activity spectra of purine analogs* [a]

Drug	Tumor					
	Ca-755	La	L1210	LL	AKATOL	RShM-5
6-Mercaptopurine	+++	−	+	−	+++	−
6-Thioguanine	+++	−	++	−	+++	+
α-Deoxythioguanosine	+++	−	++	−	+	−
6-Selenoguanosine	+++	−	+++	++	++	++

[a] *See* table 5 for definitions of symbols.

alkylating agents (Walker 256, S-45, and S-298). The drug acts on hormone-sensitive tumors similar to estrogen, a portion of which is present in its molecule. It is active against Walker 256, which is highly susceptible to alkylating drugs, but its activity is limited against S-45 and S-289 (tumors less susceptible to chlorethylamines). In the early 1960's when phenestrol was synthesized, it was tested on systems susceptible to alkylating agents. At that time (tables 5, 13), the compound displayed lower antitumor activity than other chlorethylamine derivatives and was considered unpromising. Only subsequently when the drug was used on hormone-dependent tumors was interest in it renewed. Phenestrol possesses specific estrogenic activity (table 14) and can thereby be administered to treat estrogen-susceptible tumors. The dual properties of estrogen and alklating agent contribute to the activity of phenestrol. Its analog, di(phenylacetyl) sinestrol, which does not contain the alkylating groups, had a loss of antitumor activity, as reflected in life-span and cure of rats with RMC-1 (table 15).

Estracyt, which has similar estrogenic activity (*290–293*), demonstrated activity in the treatment of patients with carcinoma of the prostate.

Studies of the effect of streptozotocin on the insular apparatus of the pancreas also represent a special interest, inasmuch as it has shown activity in the treatment of neoplasms of this organ (*27, 294*).

The recently discovered antithyroid activity of phenthyrine also opens new possibilities for the use of this drug (*132, 295*).

Doubtless, antitumor drugs with immunologic activity should be subjected to special study. In the evaluation of chanerol, which is related to phytohemagglutinin, a decisive role was played by the study of its agglutinating capacity with respect to normal (erythrocytes, leukocytes) and malignant (leukemia and solid tumor) cells. The selective agglutination of malignant cells of a number of solid tumors has been demonstrated (*174, 175*). Agglutination of erythrocytes can be prevented with a drip infusion of the drug. These studies served as a basis for the clinical testing of chanerol (*177*).

If the specificity of action of a drug is to be related to the metabolic characteristics of the tumors, a study program should include appropriate research on the subject (*296, 297*).

TABLE 13.—*Antitumor effect of phenestrol (percent tumor growth inhibition)* [a]

Drug	Tumors susceptible to alkylating agents			Hormone-sensitive tumors	
	Walker 256	S-45	S-298	RMC-1	Ca-755
Phenestrol	96.5	47	54	50–80	70
Phenester	99.5	94	90	20	33
Sinestrol	20	—	—	50–90	70

[a] Phenestrol and sinestrol are used in equimolar doses and phenester at the MTD.

TABLE 14.—*Effect of phenestrol on weight of target organs in male rats*

Drug dose	Weight of organs in mg/100 g body wt			
	Adrenals	Seminal vesicles	Ventral prostate	Testes
Control	18	487	81	1,350
100 mg phenestrol/kg	33	174	24	1,100

Previous investigations have shown that drugs with high antitumor activity in one system may also be active in several tumor systems. For this reason, in the past, a small number of tumor systems have been used in screening, but these models should be selected so that they supplement one another in sensitivity to drugs of different mechanisms of action. From the large number of experimental tumors available, it is possible to compile a number of sets of such test systems. Examples of such batteries of experimental tumors are those that have been used for primary screening of antitumor drugs at the NCI and OSC. In the NCI screening system, if the antitumor effect was evaluated not only on the basis of ILS of the animals but also by the inhibition of tumor growth, then except for drugs with estrogenic activity, 67 out of 69 drugs of clinical interest were detectable. Although the panel of tumors in the new screen has already detected several compounds with clinical activity, it is too early to assess their overall prognostic value. The OSC system allows the detection of almost all active antitumor agents (taking into account the fact that drugs with a specific type of activity are studied in special test systems). Drugs with possible specific types of activity should be investigated in special test systems.

Role of Supplementary Test Systems in the Study of Active Antitumor Drugs

An examination of the data obtained indicates that the use of some supplementary models and test systems in the study of new drugs can contribute significantly to the choice of active agents.

These may be test models which differ substantially in their properties from other models. For example, interesting information can be obtained with the use of mouse squamous cell carcinoma of the forestomach PRZh, a neoplasm insensitive to most antitumor compounds.

TABLE 15.—*Effect of sinestrol and its derivatives on RMC-1*

Drug	Dose	Life-span of animals treated with drugs	
		Days	Cure of tumors, %
Control	—	37	13
Sinestrol	0.2 mg/rat	32	23
Di(phenylacetyl)-sinestrol	100 mg/kg	31	8
Phenestrol	100 mg/kg	52	36

Against this background, the high activity of prospidine (the cure of a large proportion of the animals) acquires particular significance, inasmuch as this drug has manifested activity against human squamous cell cancer.

Also of interest is the research on the effect of drugs on mice bearing plasmacytomas. Studies with MOPC-406 have shown that an especially high response, i.e., more than 100% ILS of the treated animals (sarcolysin 132%, cyclophosphamide 113%), is exerted on this tumor by drugs active in human myeloma.

The continuing design and study of new models for experimental chemotherapy is most important. Some induced and spontaneous tumors of laboratory and especially of domestic animals (e.g., dogs) are apparently promising in this regard.

Of prognostic value are the results of research on tumors transplanted ic, such as L1210 or P388 and ependymoblastoma. In the first two models, a response against intracranially inoculated disease will be observed for drugs active against systemic disease only when the drugs pass through the blood–brain barrier. Similarly, intracranially transplanted ependymoblastoma can respond to treatment only with drugs that cross the blood–brain barrier and are active against the tumor at that site. By using L1210 and P388 inoculated ic, one can obtain information pertinent to treatment of brain metastases of a tumor susceptible to the drug used. With ic inoculated ependymoblastoma or other brain tumors, the question may be asked: Is a specific brain tumor susceptible to a drug already known to pass through the blood–brain barrier? The data in table 16 illustrate this.

The data for L1210 and P388 leukemias indicate that 5-FU, guanazole, ICFR-187, TIC-mustard, cyclophosphamide, and asaley do not pass the blood–brain barrier readily. Perhaps the poor permeability of the barrier to these drugs is the reason for their ineffectiveness on the intracranial ependymoblastoma. For verification, the sensitivity of the ependymoblastoma could also be tested following sc inoculation of the tumor.

TABLE 16.—*Susceptibility of L1210, P388 and ependymoblastoma to antitumor drugs by differing sites of inoculation and tumor localization*

Drug	ILS %				
	L1210 ip	L1210 ic	P388 ip	P388 ic	Ependymoblastoma ic
5-FU	102	33			30
Guanazole	226	28			27
ICRF-187	136	46			42
TIC-mustard	167	55			17
Cyclophosphamide	148	30			75
Spirohydantoin mustard			140–191	35	156
Asaley	58	18			42
BCNU	208	271	132–191	90–143	50
PCNU	226	235	163–172	276–318	295
Chlorozotocin	517	20			170
Fluorodopan			63–72	50	169–439

PCNU is an example of a drug which penetrates well through the blood–brain barrier and is highly effective in the treatment of animals with ependymoblastoma. Like PCNU, BCNU penetrates freely through the barrier but is only weakly active against this brain tumor (*14, 91*).

Another interesting group of drugs includes spirohydantoin mustard, chlorozotocin, and fluorodopan. The first two, judging by their effect on ic inoculated L1210 and P388, pass through the blood–brain barrier poorly, whereas fluorodopan penetrates it to a greater extent. These three compounds elicited a marked ILS for mice with intracranial ependymoblastoma that indicated this tumor possessed high sensitivity to them. This is of particular interest because one of these substances, spirohydantoin mustard, was especially designed for the treatment of brain tumors (*83, 84*). The observations raise the question whether it is possible that the therapy of some brain tumors in man with similar drugs may be accomplished even by conventional systemic administration, despite the inadequate passage of the drugs through the blood–brain barrier. An even greater effect may be achieved if such compounds can be administered directly into the brain, inasmuch as it can be expected that high concentrations of active drug will reach the target tumor site.

Also of definitive interest is the study of the effect of drugs on the same tumor inoculated by different routes. For example, it is informative for one to examine the response to drugs of L1210, P388, and B16, inoculated ip and sc. When these routes of implantation are used, the disease process and localization of tumor cells in the body varies. This may have a substantial effect on the antitumor action of the drugs, each of which has its own patterns of distribution and excretion and other characteristics.

In general, a tumor inoculated sc is less susceptible to drugs than if it is inoculated ip (Appendixes I–IV). Contributory to this is the fact that with ip inoculation of the tumor, a direct effect of the drug on the tumor cell is realized, because the drugs also are ordinarily injected into the peritoneal cavity. However, some compounds cause a greater effect against sc inoculated tumors. Thus L1210 sc was more susceptible to procarbazine, BCNU, methotrexate, and prednisone. Perhaps with this route of administration of the inoculum, the leukemia process (L1210) is localized primarily in the spleen, toward which the effect of the above drugs is directed to a considerable degree. In a study of the effect of a large number of drugs on B16 melanoma inoculated ip and sc, greater susceptibility was also found after tumor cells were injected ip. Some drugs were more effective in the treatment of sc inoculated B16: prospidine, dichlorallyl lawsone, coralyne sulfoacetate, and ICRF-187.

The tumor process in sc inoculation of L1210 and B16 differs substantially (*see* section on "Models"). The lists of substances manifesting definitive activity against sc inoculated L1210 and B16 also differ.

With various routes of inoculation of tumor cells, the localization of the tumor burden can be altered substantially, and on the basis of the results of therapeutic efficacy, implications can be drawn concerning the pharmacokinetics of the drugs.

Interesting and useful information on the drugs under evaluation can be obtained by determination of the cytotoxic effects of drugs in vitro. An important limiting factor pertains to the solubility of the materials to be tested.

Although many different systems in vitro can be used to test antitumor drugs, short-term and stationary cultures of animal and human tumors would appear to be preferable. At present, such systems are used chiefly in prescreening. About 80–85% of the compounds manifesting antitumor activity in vivo are also screened in tumor cell systems in vitro (*239, 298–301*).

The in vitro studies provide us the possibility of obtaining supplementary information on the mechanisms of action of antitumor drugs. The presence of a cytotoxic effect in vitro is indicative of a direct effect of the drug on the tumor. From the concentration of a drug resulting in a prescribed effect (e.g., the ED50) in vitro, an estimate can be made of the concentration necessary at the tumor site in vivo to suppress tumor growth. A lack of correspondence between these concentrations would indicate that either the active substance in vivo is not the drug itself but one of its metabolites or that the effect of the drug is mediated by the host.

Various tumors in vitro can react differently to the same drug; an analysis of the data indicates that these dissimilarities depend on differences in metabolism and structural–biologic characteristics of the cellular elements of the various tumors. As a result, similarities and differences in the effectiveness of drugs may provide leads concerning their mechanisms of action.

3-Deazauridine, like ara-C, strongly suppressed the growth of the same tumors: S37 and L-5178Y. It also suppresses the activity of cytidine triphosphate synthetase and thereby, like ara-C, disturbs the metabolism of cytidine nucleosides in tumor cells (*76*). The spectrum of cytotoxic effect in vitro of 6-mercaptopurine differs from that of 6-thioguanine and 6-selenoguanosine; this last compound damages the largest number of types of tumor cells. This is in agreement with the results of the study of the drugs in in vivo systems and with the above-discussed characteristics pertaining to the mechanisms of action of these compounds.

In prescreening for new antitumor agents in vitro, substances with an ED50 in vitro that did not exceed 100 μg/ml are generally considered to have evidenced sufficient activity to warrant further interest. However, as reflected in the results with guanazole, it is apparent that activity in a concentration exceeding 100 μg/ml can also represent some interest. The drug was ten times more cytotoxic in a culture of Ehrlich tumor cells than in other in vitro systems, although the ED50 was beyond the upper limits of the efficacy criterion: 100–250 μg/ml for Ehrlich tumor cells and 2,000–2,500 μg/ml for L-5178Y, S37, and NK/Ly.

Hydroxyurea exerted its greatest cytotoxic effect against Ehrlich tumor (ED50, 50 vs. 500–2,000 μg/ml for S37, L-5178Y, and NK/Ly).

Both guanazole and hydroxyurea are ribonucleotide reductase inhibitors. This enzyme is important in the biosynthesis of the deoxyribonucleotides in Ehrlich tumor cells, and it would appear that inhibition of the enzyme results in the antitumor effect of these drugs. Interestingly, inosine diglycolaldehyde, which also suppresses the activity of ribonnucleotide reductase, restrains the multiplication of L-5178Y cells most extensively and is the least effective against Ehrlich tumor. The drug also has an activity spectrum on animal tumors in vivo different from that of guanazole or hydroxyurea. This would suggest that for inosine diglycolaldehyde the primary mechanism of antitumor action is other than inhibition of ribonucleotide reductase activity.

The discovery of new drugs possessing spectra of activity in tumor culture similar to known antitumor agents would tend to indicate some similarity of mechanism underlying the cytotoxic effect. Thus the inclusion of in vitro test systems for the study of potential antitumor drugs provides an opportunity to obtain additional information concerning the drugs and may provide presumptive evidence concerning mechanisms of action of interest in clinical use.

C: POSSIBILITY OF PREDICTING THE SPECTRUM OF ANTITUMOR EFFECT OF DRUGS ON THE BASIS OF EXPERIMENTAL DATA

The results with antitumor drugs in experimental systems (table 5) and in patient treatment (table 7) show that correspondence of activity of compounds for various types of tumor is not complete.

Some antileukemia drugs (myleran, phenthyrine, prednisolone) do not inhibit the growth of most experimental leukemias but do inhibit the growth of other forms of animal tumors (table 17). Table 18 provides an example in which there is no clear correlation of the effect of drugs on the same types of solid human and animal tumors.

Nevertheless, analysis of the present material does permit an evaluation of possible approaches to the prediction of the spectrum of activity of drugs against human tumors on the basis of experimental data.

The differences in susceptibility of human tumors to chemotherapeutic agents, like that of animal tumors, is undoubtedly related to their metabolic characteristics (*129, 286, 302–306*).

The pharmacokinetic characteristics of drugs and their metabolic transformations in the host, as well as the kinetics of cellular reproduction of the tumor, may exert important influences on the therapeutic results. However, the structural–biochemical profile of the neoplasm is nevertheless decisive for the outcome of the therapy. Even when a high concentration of the active form of the drug is delivered to the tumor site and when the cells are in a mitotic phase susceptible to the chemotherapy, the tumor cells will remain viable if 1) cell membranes provide an

TABLE 17.—*Activity of some antitumor drugs in experimental systems* [a]

Drug	Tumor										
	L1210	P388	La	MOPC-406	Ca-755	LL	B16	AKATOL	RShM-5	S37	S180
Myleran	−	−	−	−	+	−	−	+	−	++	−
Phenthyrine	−	++	−	−	+++	++	++	−	+	++	−
Prednisolone	−	−	−	−	++	+	+	+	−	+	

[a] *See* table 5 for symbol definitions.

effective barrier to drug entry, 2) cells contain no targets for the antitumor agent, 3) cells are capable of avoiding the metabolic block created by the drug, or 4) they easily correct for the deficiences created, etc.

It is most important to enlarge on and systematize the existing data pertaining to the structural–biochemical differences between the various types of animal and human tumors.

An analysis of clinical data, despite their incompleteness, permits examination of any regular patterns in the susceptibility of the individual tumor types to chemotherapeutic agents.

Some similarity is apparent in the response of clinical mammary gland and ovarian cancers and possibly uterine cervix tumor to antitumor drugs. Inasmuch as the proliferation and functional activity of organs from which these tumors develop are regulated by the same hormones, the response to which may be governed by the presence in the cells of hormone receptors, this regulation may underlie any observed similarities. Tumors of the mammary gland in rats have been used successfully in the search for drugs effective in breast cancer, and it is suggested that these and related models may also be valuable in the screening of chemotherapeutic agents for ovarian cancer and cancer of the uterine cervix (*273, 307–311*). The value of screening for induced cancer of the ovary in laboratory animals has not been clarified.

Trapeznikov et al. (*312*) reported the presence of specific antigens for melanoma, and for this tumor, the use of immunotherapy is possible. In one study alteration of the tumor was accomplished by means of attaching new chemical determinant groups to the cell; some antitumor drugs, e.g., sarcolysin, may be used for this purpose. Antitumor agents can also cause activation of the cytotoxic function of the lymphocytes directed at tumor cells (*313*). Dactinomycin is one of the drugs which has evidenced this property and, like sarcolysin, it has demonstrated some activity in patients with melanoma (table 7). Of the antibiotics, olivomycin also exerted activity against melanoma, which is interesting because its mechanism of action has features in common with dactinomycin (*162*).

Lung cancer (small cell) has not been susceptible to all of the drugs that demonstrated some effect on melanoma. Also, some drugs have acted against small cell lung cancer but have been inactive in melanoma.

Some compounds which have shown activity in small cell lung cancer are immunosuppressants (cyclophosphamide, methotrexate, nitrogen mustard). Also, in patients with this form of cancer an ACTH-like hormone, ectopic ACTH, is often produced by the tumor (*314–317*). In these patients, the function of the adrenals is altered, and that of the thyroid is reduced, i.e., the functions of organs closely associated with the immune response have been altered (*314, 315, 318, 319*). Some relationship may exist between the above-noted metabolic characteristics in patients with lung tumor and the susceptibility of small cell lung cancer to drugs that influence the corticosteroid function of the adrenals. Some experimental tumors known to be susceptible to corticosteroids are Ca-755, AKATOL, and those of the transplantable C3H mammary gland. Drugs that produced an effect in human lung cancer actively suppressed the growth of either Ca-755 or AKATOL, or both (table 5). In lung cancer, a relationship may exist between the metabolic influences of

TABLE 18.—*Effect of drugs on carcinomas and melanomas of animals and man* [a]

Drug	Carcinoma and/or melanoma							
	Animals				Man [b]			
	Ca-755	LL	AKATOL	B16	Mammary gland	Large intestine	Lung	Melanoma
Methotrexate	+++	+	+++	+++	+	+	+	−
5-FU	+++	++	−	++	+	+	−	−
6-Mercaptopurine	+++	−	+++	++	−	−	−	
Adriamycin	+++	−	+	+	+	−	+	−
Dactinomycin	++	−	+	+		−		+
DTIC	+	+	++	+++	−	−	−	+

[a] *See* table 5 for symbol definitions.
[b] *See* table 7.

this tumor and its susceptibility to antitumor drugs; this subject is worthy of further investigation.

Knowledge of the metabolic characteristics of human tumors and of their interrelationships with the host may aid in the prediction of the activity spectra of new chemotherapeutic agents. It also seems clear that the experimental tumor systems may detect properties of drugs which are decisive for activity in various forms of human tumors. Various properties of a drug may contribute to activity against human tumors and these will be most readily detected not by one but by a number of different experimental systems. In view of this, there would appear to be an advantage in having the prediction of the antitumor activity spectra of drugs based on the sum total of observations in a large number of different types of models. Some aspect of hormone activity may have decisive significance for the reaction of drugs against certain types of tumors, immunologic activity in others, and different characteristics of the mechanism of action in still others.

Elucidation of the pharmacokinetics of the drugs can be of substantial assistance in predicting the effect of drugs on tumors and on the host. As stated earlier, the possibility of creating in a susceptible tumor situated in a certain region of the body a concentration of the drug necessary for an effect depends on the distribution of the compound in the body. This is well illustrated by the above-listed examples of substances, some of which penetrate the blood–brain barrier and others which do not (table 16).

A correspondence between the distribution of drugs in the organism and their antitumor effects has been found for streptozotocin (*31*), prospidine (*140*), bleomycin (*320, 321*), ara-C (*322*), and for other antitumor agents. Manifestation of the antitumor effect may be influenced by both the concentration of drug and the time of exposure at the tumor site, although the level of drug need not be high (*323*). The prolonged maintenance of an effective concentration of the drug in the tumor appears highly important for phase-dependent drugs. Prolonged exposure results in an effect of the agent on the maximum possible number of tumor cells, inasmuch as the latter are continuously entering into the phase of greatest susceptibility to the drug as they move through the cell cycle (*265, 268*).

The relationship between the distribution and elimination of drugs from the normal organs and tissues and the toxic effect on the host is evident. More rapid alleviation of the toxic effect of the substance on normal tissues compared with the tumor may contribute to an increase in selective damage to the neoplasm.

An important role in the resultant biologic effects of drugs is played by their metabolism in the host and in the tumor. A number of agents are biologically inert until they are transformed into active products (e.g., cyclophosphamide). The study of the metabolism of antitumor drugs in the organism and in tumors is necessary to determine means for control of the activity of these substances. Ho (*39*) and Camiener (*324*) have reported on the stabilization of ara-C when using tetrahydrouridine to improve its activity. Investigation of the metabolism of this drug led to the preparation of numerous compounds that did not undergo deamination, e.g., cyclocytidine, etc. (*39, 325*).

To date, pharmacokinetic studies appear to have contributed only a small measure of their potential to the selection of antitumor drugs. Clearly, further developments in pharmacokinetics and investigations of the mechanisms of action will broaden the selection of new and more effective agents for patient therapy.

The use of human tumors growing in athymic mice for screening and chemotherapeutic investigations may prove highly beneficial in the translation of preclinical drug activity to the treatment of patients. The new screening panel at the Division of Cancer Treatment, NCI (text-fig. 3), is designed to determine whether the incorporation of human tumors as test models will yield a higher incidence of new drugs that are more effective against clinical neoplasia. Also, it may improve predictability of drugs active against specific types of tumors.

Overall, the analysis of the data obtained in the preclinical screening systems emphasizes that definitive relationships may be established between the structural characteristics and metabolic patterns of animal and human tumors and their susceptibility to antitumor agents.

Chapter IV: Ranking Drugs for Clinical Trials[1]

The ultimate goal of screening activity with potential chemotherapeutic agents is identification of compounds that are effective in the clinical treatment of various human tumors. For this goal to be achieved, it is necessary that therapeutic results obtained with animal tumor models are correlated in some useful way with results achievable in patient therapy. To the extent that such correlations exist and can be identified, they can 1) lend validity to the concept of screening, 2) facilitate comparative evaluations of various screening models, and 3) lead to useful predictions of clinical results.

In this chapter we shall discuss two related methods of prediction methodology: One makes use of the statistical theories of multiple correlation and regression (regression method), and another is based on more general concepts of pattern recognition The regression method has the advantage of requiring only data related to animal testing and clinical results, but the mathematical models are restricted by the modest number of compounds for which such information exists. The pattern recognition method uses additional chemical and biologic information about each compound and does not require that complete information be available.

In the development of methodology, data have been used that do not necessarily constitute the most complete or accurate information desired. The results of animal screening are only partial in that they do not reflect the use of the new animal screens, e.g., human xenografts in nude mice. The responses were supplied by clinical investigators in the United States and Soviet Union with the use of current literature. Although such data represent the best that could be made available at the time of statistical analysis, it is generally conceded that they can reflect only qualitative consensual judgments and should not be regarded as final authoritative clinical evaluations of anticancer compounds.

Research conducted with these provisional data by the regression method has yielded results that are encouraging relative to the possibility for correlating animal with clinical results ("Regression Method"). With the mathematical models developed by this research, predictions have been made of clinical activity against certain specific tumors for compounds for which complete animal test results are available but which have yet to be evaluated in man. Such predictions should be regarded as illustrative of the use of the methodology until more comprehensive data become available.

Application of the pattern recognition method (described in "Methods of Prediction") requires the accumulation of more general data concerning potential anticancer compounds than has heretofore become available. Initial efforts at application, necessarily limited by the amount of accessible data, are summarized and discussed in the section on "Pattern Recognition Method."

A: METHODS OF PREDICTION

The problem of predicting the clinical activity of antitumor compounds can be reduced to a form convenient for the application of mathematical methods. Suppose we are given a collection of observations or data points so that each point represents a set of attributes or properties of a different compound. These attributes can consist of 1) results determined when the compound is used in one or more animal tumor models, 2) biologic or chemical properties of the compound, or 3) both kinds of information. Such a data point is said to have dimension n if it includes n distinct attributes. Furthermore, we shall assume that l such data points are available. The general problem for us then is to predict the activity of a new compound not yet clinically tested. We can achieve this by dividing the n-dimensional space consisting of the l known data points into two subspaces, one associated with clinical activity against a given human tumor and the other with inactivity.

The method of regression is one of the classical means for solving this problem. It leads to a formula or "discriminant function" with a rule for classification. Thus if the data point for a given compound is substituted in this formula, the value obtained can be used with the classification rule to conclude whether the point lies in the space of "actives" or in that of "inactives." In theory, the development of the discriminant function requires the existence of two conditions: 1) The sets of active and inactive data points belong to multivariate normal populations with identical covariance matrices; and 2) the number of data points must be large relative to the number of attributes comprising each data point.

In practice, modest deviations from the first condition usually cause few difficulties. However, the second condition, generally tends to restrict the number of attributes as well as the form of the discriminant function. Several newer methods of classification have been proposed under

Abbreviations: NCI = National Cancer Institute; OSC = Oncological Scientific Center; DTIC = dacarbazine; ara-C = cytosine arabinoside; CCNU = 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea; Me-CCNU = 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea; *cis*-PT(II) = *cis*-platinum(II) diamminedichloride; BCNU = 1,3-bis(2-chlorethyl)-1-nitrosourea; LL = Lewis lung (tumor).

[1] This chapter was prepared by I. Miller, V. N. Vapnik, and T. G. Glazkova.

the general theory of "pattern recognition" (*326, 327*) that will assist us to overcome these difficulties. These methods are proposed to remove the retrictive conditions required for the classical approach; in particular, they allow the potential use of much more information concerning the attributes of each compound.

The problem of pattern recognition appeared at the end of the 1950's and consists of the following: $x_1^*, \ldots, x_1^*$. A certain number of examples are available of compounds (data points) that belong to one class and some that belong to a second class: $\bar{x}_1^*, \ldots, \bar{x}_{l_2}^*$. One must construct a rule $F(x)$, with the help of which any compound can be classified as accurately as possible into one of two classes.

For this purpose, one portion of the compounds has been tested on human beings (this fact is marked with an *asterisk*). Active compounds are denoted by x^* and inactive by $\bar{x}^*$. The required function, $F(x)$, would give the value of 1 and 0 for compounds belonging to the first and second class, respectively.

We refer to the problem of constructing a function that separates the compounds of the first and second class with as few errors as possible as "training." The central question of the prediction problem is to determine whether an achieved good separation of the training sequence into two classes guarantees a high quality of classification of new compounds.

Theoretical results show that if the number of training points is large and the "complexity" of the constructed function $F(x)$ is not great, then the quality of the resulting predictions will be approximately the same as the quality of the separation of the training sequence into two classes. If the complexity is large, then even if the training points are divided unerringly, the classification of the new examples cannot be considered successful.

For ascertainment that the classification rule discovered is satisfactory, it is necessary not only that the given examples be correctly divided in accordance with this rule but also that the rule itself be simple; these two requirements are contradictory. The more complex the determining rule the more accurately the training sequence can be divided with its help.

To obtain maximum accuracy in future classification, one must reach a compromise between the complexity of the determining rule and the accuracy that can be obtained for a rule of known complexity in the classification of given compounds.

When mentioning "complexity" of the determining rule, we have appealed to intuition. The concept of complexity of a function is a subtle one and we will not define it here. However, theory shows that it is possible to reduce complexity with only coarse descriptions for each parameter. For instance, with respect to animal test results, we could use the description:

1 = if prolongation of life-span extends beyond a certain standard;

0 = if prolongation of life-span is equal to the standard;

−1 = if prolongation of the life-span is less than the standard.

What then is preferable; is it better to seek meaning in any small change in the value of a parameter and to construct a rule on the basis of a small number of parameters, or to try to take into account as many parameters as possible but to make use only of their rough (qualitative) characteristics? The answer to this question can be given only as a result of experimental research. Nevertheless, taking only the qualitative characteristics of each parameter into consideration is consistent with our objectives of a qualitative prediction (active or inactive compound).

Therefore, to increase the accuracy of the construction of a determining rule for prediction of the activity of compounds, one can either 1) reach the required compromise between the complexity of the determining rule and the accuracy of the classification of the training sequence given for the construction of the rule, or 2) increase the number of parameters used in the construction of the rule without increasing the complexity of the rule by using qualitative data concerning the value of each of these parameters.

Obtaining a formula for the determining rule constitutes a complete solution to the problem. However, in practice we are faced with a far more modest problem, i.e., the classification of given compounds as active or inactive. It is not necessary to find a general formula for the rule to classify any compound. This is an important idea because finding the general formula is a considerably more complex problem than the one set before us: the classification of compounds of interest.

Moreover, the theory of classification shows that better results may be achieved if we exclude certain compounds from the group to be classified. Although the excluded compounds will not be classified, those that remain will be classified with the highest obtainable degree of accuracy.

B: REGRESSION METHOD: RESULTS AND PREDICTIONS

The regression method for ranking compounds is based on the development of mathematical models or formulas which relate animal test data for chemotherapeutic agents to the results of clinical trials with these agents. The data required to estimate these models consist of both complete screening results in as wide a variety of animal models as possible and clinical results against specific human tumors. Each compound for which a complete set of such data exists gives rise to a data point, and a ranking model is estimated for a specific human tumor type by methods of multiple regression, whenever sufficient data points become available.

Available Data

All available clinical studies in which compounds have been tested as single agents were reviewed by clinicians at the NCI or at the OSC. Consideration was given to the number of patients with either a complete or a partial remission (patients responding) as well as the number of patients who could be evaluated (those who received sufficient drug in a well-defined therapy regimen). Based

TABLE 19.—*Screening and clinical data summary*

Compound	NSC No.	Average T/C value for mouse tumors					Clinical evaluations			
		L1210 ip	L1210 sc	P388	B16	LL	Breast	Colon	Lung	Melanoma
Methotrexate	740	187	246	228	108	113	S++	S+	S++	S−
Myleran	750	109	104	112	98	107	NE	NE	S−	NE
6-Thioguanine	752	171	157	132	125	121	NT	S−	NT	NT
6-Mercaptopurine	755	159	156	125	115	110	S−	S−	S−	S−
Nitrogen mustard	762	153	121	209	186	116	S++	S−	S++	S−
Cycloleucine	1026	140	127	129	147	113	NE	(NE)	NE	NE
Dactinomycin	3053	136	125	271	167	121	NE	S−	NE	S+
Stilbestrol	3070	102	101	110	102	107	NT	NT	NT	NT
Chlorambucil	3088	130	110	170	130	116	S+	S−	NE	S−
Thio-TEPA	6396	160	166	163	123	114	(NE)	(NE)	NE	(NE)
Phenylalanine mustard	8806	198	152	336	176	123	S++	S−	NE	S−
Triethylenemelamine	9706	177	158	230	136	135	NE	NE	(NE)	NE
Prednisone	10023	105	128	104	119	114	NE	NT	NT	NT
Hexamethylmelamine	13875	107	108	109	111	109	S++	S+	S++	S−
17256E	17256E	99	109	108	118	111	NE	NE	NE	NE
Testosterone	17591	107	104	113	133	117	NT	NT	NT	NT
5-FU	19893	172	163	178	130	118	S++	S++	S−	S−
Mithramycin	24559	108	107	137	115	120	NE	NE	S−	S−
Cyclophosphamide	26271	324	288	296	152	158	S++	S+	S++	S−
Provera	26386	103	92	103	113	134	NE	NT	NT	NT
Mitomycin C	26980	153	125	198	165	120	S++	S++	S+	S−
Floxuridine	27640	155	147	196	142	127	S++	S++	S−	NE
Hydroxyurea	32065	253	147	120	127	116	S−	S−	S+	S−
6-Azauridine	32074	142	126	131	110	117	NT	NT	NT	NT
Trimethylcolchicinic acid methyl ether	36354	122	132	131	113	116	NE	S−	S−	S−
Streptonigrin	45383	112	103	133	132	101	(NE)	S−	S−	(NE)
DTIC	45388	150	153	129	130	118	NE	S−	S−	S++
Vinblastine	49842	133	113	208	171	121	S+	S−	S−	S−
Tubercidin	56408	119	—	141	115	104	NE	S−	NE	NE
Porfiromycin	56410	164	125	219	134	103	NE	S−	S−	NE
Azotomycin	56654	165	106	163	109	107	NE	S+	S−	(NE)
Chromomycin A_3	58514	134	105	198	135	124	NT	NT	NT	NT
Ara-C	63878	448	315	215	131	123	NE	S−	S−	S−
Vincristine	67574	131	120	251	160	118	S+	S−	S−	S−
1-Acetyl-2-picolinyl-hydrazine	68626	112	115	105	102	89	NE	S−	NE	NE
5-Trifluoromethyl-2'-deoxyuridine	75520	155	155	121	116	144	(NE)	NE	NT	NE
Procarbazine	77213	154	163	155	124	102	NE	S−	S+	S−
CCNU	79037	502	418	241	203	123	S−	S−	S++	S+
Daunomycin	82151	137	126	192	211	119	NE	NE	NE	NE
TIC-mustard	82196	356	334	282	165	122	NE	S−	NT	S−
Streptozotocin	85998	136	131	167	125	106	NE	S−	NE	NE
Dibromomannitol	94100	113	106	135	130	109	NT	NT	NT	NT

TABLE 19.—*Screening and clinical data summary (continued)*

Compound	NSC No.	Average T/C value for mouse tumors					Clinical evaluations			
		L1210 ip	L1210 sc	P388	B16	LL	Breast	Colon	Lung	Melanoma
Me-CCNU	95441	360	343	245	190	147	S−	S+	S+	S+
Camptothecin	100880	212	152	170	134	141	NT	S−	NT	S−
Yoshi-864	102627	310	150	291	189	113	NE	NE	S−	S−
5-Azacytidine	102816	225	172	232	137	115	S−	S−	NE	NE
Dibromodulcitol	104800	127	129	127	125	115	S+	S−	S+	S+
L-Asparaginase	109229	112	134	134	109	93	NE	NE	NE	NE
Iphosphamide	109724	284	260	221	142	147	S+	S−	S+	NT
cis-Pt(II)	110875	163	148	220	181	114	NE	S−	NE	NE
Adriamycin	123127	170	156	295	259	120	S++	S−	S++	S−
Bleomycin	125066	110	110	128	142	147	S−	S−	S−	S−
ICRF-159	129943	203	176	196	129	121	NE	S+	S−	NE
BCNU	409962	346	447	282	198	138	S+	S+	S+	S+
Sarcolysin	14210	173	—	300	273	110	S+	S−	S−	S+
Digitonin	23471	102	—	101	109	129				
Dopan	44629	144	130	197	145	126	NT	NT	NT	NT
Fluorodopan	73754	129	—	150	143	122	NT	NT	NT	NT
Olivomycin	76411	166	131	223	160	97	NT	NT	S−	S+
Reumycin	99733	104	—	100	118	—				
Ftorafur	148958	180	168	136	133	119	S+	S+	NT	NT
1H-Pyrazolopyrimidine riboside derivative	154819	117	—	—	—	—				
Prospidine	166100	111	114	156	176	—	S+	NT	S−	S+
Asaley	167780	158	160	185	121	119	S+	S−	S−	NE
Diiodobenzotepa	167781	160	161	221	145	117	S+	NT	NT	NT
Carminomycin	180024	133	—	176	125	103	S+	NT	NT	NT
Palphicerin	183734	130	128	245	132	104	NT	NT	NT	NT
Distron	183735	111	121	195	123	121	NT	NT	NT	NT
Phenestrol	183736	106	—	107	108	104	NT	NT	NT	NT
Chanerol	183737	106	—	100	110	105				
Colchizin	183738	110	—	160	118	102				
Aton	196869	102	—	113	98	—				
Tomizin	216134	101	102	105	200	122	NT	NT	NT	NT
Fotrin	216135	160	—	248	181	116	NT	NT	NT	NT
Histare	269141	136	—	241	144	113				
Variamycin	269146	115	—	170	134	128				
Diazan	271276	145	—	170	143	—				
Glucomannan	275652	96	—	104	102	102				
Agavoside	275653	97	—	100	110	98				
Funkioside	275654	108	—	95	103	136				
Vitalboside	275655	101	—	99	88	120				
Klophocyl	275659	147	—	206	—	—				
Methylnitrosourea	23909	188	161	157	144	124	NT	NT	S+	S+
Dioxadet	275656	195	—	214	178	119	NT	NT	S+	NT
Imidaphen	275657	155	—	187	159	114				
Phenthyrine	275658	124	—	171	164	119	NT	NT	S−	NT

on this information, each compound was evaluated for activity against each of 17 solid human tumors according to the following designations:

S++ = definite clinical activity
S+ = some clinical activity
S− = no clinical activity
NE = evaluation not possible
(NE) = evaluation not possible but preliminary evidence of activity present

The resulting clinical evaluations are shown in table 19 only for those human tumors for which sufficient data are currently available for use in the statistical analysis. They reflect the response rates, definition of response, and a consensus of clinical judgment as to whether a particular compound was adequately evaluated and, if so, whether it was active. In making such activity judgments, the clinicians involved took into account the known sensitivity or resistance to chemotherapy of each tumor type.

The following five mouse screening systems were chosen on the basis of adequacy of available data and accuracy and consistency of screening results: leukemia L1210, ip and sc; P388; B16 melanoma; and LL carcinoma. For each compound, a representative value of T/C was obtained by an average of optimum values in available animal tests against each animal tumor system that passed several statistical criteria for acceptability. The resulting animal test data also are displayed in table 19.

Methodology

Each ranking model equation, representing the multivariate correlation between the five animal test results and the corresponding clinical results, has the following form: $y = f(x_1, x_2, x_3, x_4, x_5)$, where y is the clinical evaluation, and x_1, x_2, x_3, x_4, and x_5 are the natural logarithms of T/C for the L1210 ip, L1210 sc, P388, B16, and LL screens, respectively. Statistical analysis has shown that the S+ and S++ compounds do not differ significantly in their correlation with animal test results; accordingly, these two groups were combined as active compounds, to which a y-value of 1 was assigned. All inactive compounds (S−) were assigned y-values of 0, and compounds having the clinical evaluations NE or (NE) or NT (not tested) for any given human tumor type were not included in the model construction phase.

Sufficient data currently exist to facilitate estimation of ranking models for 4 human tumors, i.e., those of the breast, colon, lung, and melanoma. The equations of the ranking models so derived are shown in table 20. Each value of R^2 shown in this table gives the proportion of the original variability in the values of y that is explained by the corresponding equation. (The square root of R^2 is the magnitude of the multiple correlation between the clinical and screening results as combined by the equation.) These equations represent nonlinear polynomials; because they express purely empirical relationships between clinical and screening results, they are not suitable for extrapolation purposes, nor do they portray fundamental laws governing the exact mathematical relationships among screening systems.

TABLE 20.—*Ranking models for 4 human solid tumors*

A) Breast tumor ($R^2 = 0.64$)
$$y = 0.06522 - 0.13105\,x_1 + 0.59817\,x_2 + 2.59621\,x_4 + 2.09037\,x_5 - 4.38727\,x^2_1 + 3.82884\,x_1x_2 + 16.94498\,x_1x_5 - 14.27530\,x_2x_5 - 12.42208\,x_4x_5$$

B) Colon tumor ($R^2 = 0.42$)
$$y = 0.36417 + 1.10819\,x_1 - 0.96246\,x_2 + 0.18619\,x_3 - 1.47203\,x_4 - 0.08094\,x_5 - 0.93125\,x^2_1 - 11.84980\,x^2_5 + 1.55235\,x_2x_3 - 2.70312\,x_3x_4 + 17.88618\,x_4x_5$$

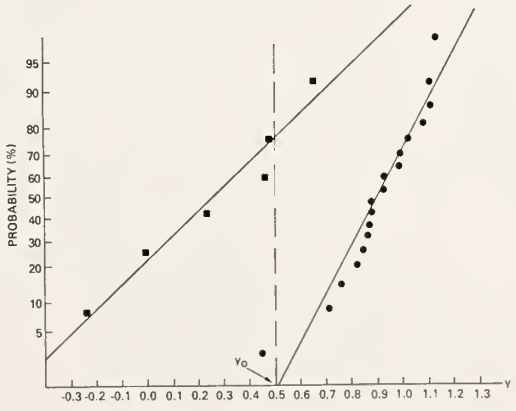
C) Lung tumor ($R^2 = 0.42$)
$$y = 0.52383 - 0.10654\,x_3 + 1.73032\,x_4 - 5.03105\,x_5 - 6.35973\,x_3x_4 + 8.31578\,x_3x_5 + 5.42329\,x^2_4$$

D) Melanoma tumor ($R^2 = 0.53$)
$$y = -0.27988 - 0.64758\,x_1 + 0.67951\,x_2 + 2.57532\,x_3 - 1.29787\,x_4 + 1.59360\,x_5 - 2.99911\,x_2x_3 + 2.51038\,x_2x_4 + 7.53211\,x_2x_5 - 8.23978\,x_3x_5$$

Classification of Compounds

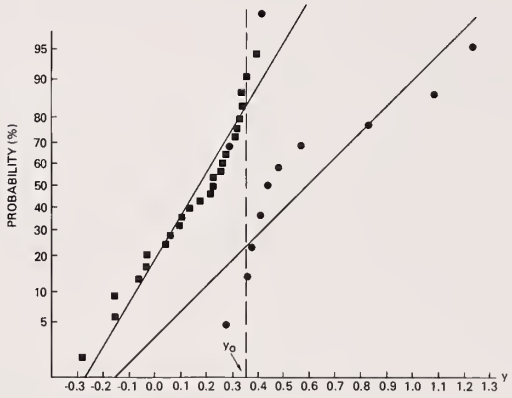
For each compound (data point) used to develop a given ranking model, a predicted value of y ($\hat{y}$) can be derived by a substitution of the corresponding values of x_1, x_2, x_3, x_4, and x_5 in the equation for that model. The probability distribution of these $\hat{y}$-values is graphed separately for clinically active (S++ and S+) and inactive (S−) compounds in text-figures 10–13.

The varying degrees of separation between the lines shown in text-figures 10–13 illustrate the differing abilities of these ranking models to discriminate between clinically active and inactive compounds. For example, in text-figure 10, the overlap between the two sets of data points contains only 2 points. If the cutoff value $y_o = 0.5$ is chosen to classify any compound as a predicted active or inactive depending on whether $\hat{y}$ is greater or less than 0.5 for that compound, 2 of the 24 compounds are thus misclassified. Estimates of the relative frequencies of misclassification errors are found by the observation that the inactive (*upper*) line intersects the line $y = 0.5$ at the ordinate 0.75 and the active line intersects at about 0.01.



TEXT-FIGURE 10.—Distribution of $\hat{y}$-values for breast tumor; *closed circles* = S+ and S++ compounds; *solid squares* = S− compounds.

Thus the probability that an inactive compound will erroneously be classified as active (false positive) is $1 - 0.75 = 0.25$, and the probability that an active compound will be classified as inactive (false negative) is 0.01. Results of classifying compounds used to construct all four ranking models are summarized in tables 21–24.



TEXT-FIGURE 11.—Distribution of $\hat{y}$-values for colon tumor. *See* text-figure 10 legend for symbol designations.

TABLE 21.—*Classification of compounds used in the regression methodology against breast tumor*

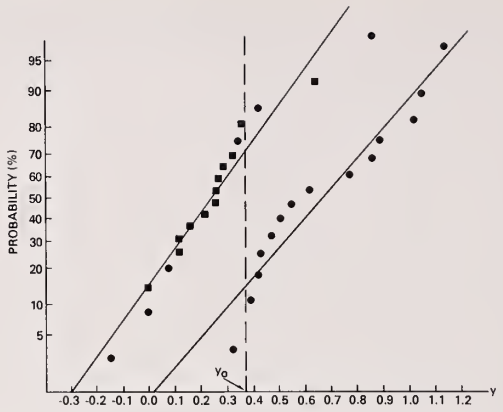
Activity	$\hat{y} < 0.5$	$\hat{y} > 0.5$
S++, S+	1	17
S−	5	1

Compounds correctly classified

Iphosphamide	S+	Chlorambucil	S+
Cyclophosphamide	S++	BCNU	S+
Adriamycin	S++	Dibromodulcitol	S+
Nitrogen mustard	S++	Ftorafur	S+
Methotrexate	S++	Asaley	S+
Mitomycin C	S++	Diiodobenzotepa	S+
Vinblastine	S+	5-Azacytidine	S−
Vincristine	S+	Me-CCNU	S−
Phenylalanine mustard	S++	Bleomycin	S−
Floxuridine	S++	CCNU	S−
5-FU	S++	Hydroxyurea	S−

Compounds misclassified

False negative: Hexamethylmelamine	S++
False positive: 6-Mercaptopurine	S−
Errors of misclassification:	
Probability of false negative	0.008
Probability of false positive	0.245



TEXT-FIGURE 12.—Distribution of $\hat{y}$-values for lung tumor. *See* text-figure 10 legend for symbol designations.

TABLE 22.—*Classification of compounds used against colon tumor*

Activity	$\hat{y} < 0.35$	$\hat{y} > 0.35$
S++, S+	1	10
S−	24	3

Compounds correctly classified

BCNU	S+	Hydroxyurea	S−
Me-CCNU	S+	Camptothecin	S−
Methotrexate	S+	Trimethylcolchicinic acid methyl ether	S−
Azotomycin	S+		
Floxuridine	S++	Streptozotocin	S−
ICRF-159	S+	Phenylalanine mustard	S−
Cyclophosphamide	S+	1-Acetyl-2-picolinyl-hydrazine	S−
5-FU	S++		
Mitomycin C	S++	Procarbazine	S−
Ftorafur	S+	Dactinomycin	S−
DTIC	S−	Nitrogen mustard	S−
Chlorambucil	S−	Vincristine	S−
Bleomycin	S−	Porfiromycin	S−
6-Thioguanine	S−	Platinum salt	S−
Dibromodulcitol	S−	Streptonigrin	S−
Vinblastine	S−	Ara-C	S−
6-Mercaptopurine	S−	CCNU	S−
Iphosphamide	S−	Adriamycin	S−

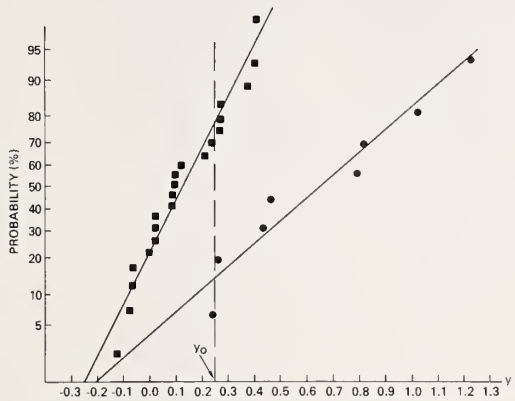
Compounds misclassified

False negative: Hexamethylmelamine	S+
False positives: TIC-mustard	S−
5-Azacytidine	S−
Asaley	S−
Errors of misclassification:	
Probability of false negative	0.227
Probability of false positive	0.164

Ranking of Compounds Not Clinically Evaluated

Any compound tested in each of the 5 animal systems can be ranked with respect to its predicted clinical activity against a specific human tumor for which a suitable ranking model has been estimated. The ranking is achieved by substitution of values of x_1, x_2, x_3, x_4, and x_5, which represent the animal test results for a given compound in the appropriate model equation (table 20) for a given human solid tumor. This will result in a value of $\hat{y}$, the index of predicted clinical activity. If the resulting index of predicted clinical activity exceeds the cutoff value for that human tumor (cutoff values are shown in text-figs. 10–13), that compound is predicted to be clinically active against the given tumor.

The results of applying the ranking model equations to compounds not yet clinically evaluated against each human solid tumor (breast, colon, lung, and melanoma) are shown in table 25, in which the compounds are listed in rank order, beginning with those having the highest values of $\hat{y}$. The clinician can make use of these predictions by starting at the top of the list and applying other purely clinical considerations (e.g., toxicity, tumor stage) in a process of elimination. Such a process would produce a compound (or set of compounds) that meets the clinical desiderata and at the same time has maximum predicted activity on the basis of animal test results.



TEXT-FIGURE 13.—Distribution of $\hat{y}$-values for melanoma. *See* text-figure 10 legend for symbol designations.

TABLE 23.—*Classification of compounds used against lung cancer*

Activity	$\hat{y} < 0.37$	$\hat{y} > 0.37$
S++, S+	1	13
S−	15	3

Compounds correctly classified

Adriamycin	S++	6-Mercaptopurine	S−
Me-CCNU	S+	Azotomycin	S−
Cyclophosphamide	S++	5-FU	S−
CCNU	S++	Ara-C	S−
Nitrogen mustard	S++	ICRF-159	S−
BCNU	S+	Myleran	S−
Mitomycin C	S+	Trimethylcolchicinic acid methyl ether	S−
Iphosphamide	S+		
Procarbazine	S+	Vincristine	S−
Hydroxyurea	S+	Mithramycin	S−
Methotrexate	S++	Bleomycin	S−
Dibromodulcitol	S+	Porfiromycin	S−
Methylnitrosourea	S+	Yoshi-864	S−
		Asaley	S−
Floxuridine	S−	Olivomycin	S−

Compounds misclassified

False negative:	Hexamethylmelamine	S++
False positives:	Streptonigrin	S−
	Vinblastine	S−
	DTIC	S−
Errors of misclassification:		
Probability of false negative		0.134
Probability of false positive		0.312

TABLE 24.—*Classification of compounds used against melonoma*

Activity	$\hat{y} < 0.25$	$\hat{y} > 0.25$
S++, S+	1	7
S−	15	6

Compounds correctly classified

Dactinomycin	S+	Hexamethylmelamine	S−
DTIC	S++	Mithramycin	S−
CCNU	S+	Cyclophosphamide	S−
Me-CCNU	S+	Mitomycin C	S−
BCNU	S+	Hydroxyurea	S−
Olivomycin	S+	Vinblastine	S−
Methylnitrosourea	S+	Ara-C	S−
Methotrexate	S−	TIC-mustard	S−
Nitrogen mustard	S−	Yoshi-864	S−
Chlorambucil	S−	Adriamycin	S−
Phenylalanine mustard	S−	Bleomycin	S−

Compounds misclassified

False negative:	Dibromodulcitol	S+
False positives:	6-Mercaptopurine	S−
	5-FU	S−
	Trimethylcolchicinic acid methyl ether	S−
	Vincristine	S−
	Procarbazine	S−
	Camptothecin	S−
Errors of misclassification:		
Probability of false negative		0.134
Probability of false positive		0.230

TABLE 25.—*Ranking of compounds not clinically evaluated*

Tumor	Predicted active		Predicted inactive	
	Compound	$\hat{y}$-value	Compound	$\hat{y}$-value
Breast	Camptothecin	1.49	Distron	0.46
	Platinum salt	1.12	17256E	0.40
	Chromomycin A_3	1.08	Porfiromycin	0.35
	Triethylenemelamine	1.06	Prednisone	0.33
	5-Trifluoromethyl-2'-deoxyuridine	1.06	Stilbestrol	0.26
	Daunomycin	1.05	Myleran	0.22
	Provera	0.98	1-Acetyl-2-picolinylhydrazine	− 0.02
	Cycloleucine	0.93	Azotomycin	− 0.14
	Methylnitrosourea	0.93	Ara-C	− 0.41
	Dactinomycin	0.91	Yoshi-864	− 1.12
	Dopan	0.90		
	6-Thioguanine	0.88		
	ICRF-159	0.85		
	Procarbazine	0.84		
	DTIC	0.83		
	Palphicerin	0.83		
	Thio-TEPA	0.82		
	Streptonigrin	0.75		
	Olivomycin	0.75		
	TIC-mustard	0.74		
	6-Azauridine	0.73		
	Dibromomannitol	0.73		
	Streptozotocin	0.71		
	Testosterone	0.67		
	L-Asparaginase	0.61		
	Mithramycin	0.58		
	Trimethylcolchicinic acid methyl ether	0.56		
	Tomizin	0.56		
Colon	Tomizin	1.24	Stilbestrol	0.33
	Methylnitrosourea	0.51	Chromomycin A_3	0.33
	Dopan	0.45	6-Azauridine	0.32
	Triethylenemelamine	0.41	Daunomycin	0.29
	Testosterone	0.41	Dibromomannitol	0.22
	Myleran	0.39	17256E	0.19
	Cycloleucine	0.37	Mithramycin	0.19
	Thio-TEPA	0.36	Distron	0.19
	Diiodobenzotepa	0.35	Prednisone	0.12
			L-Asparaginase	0.02
			Palphicerin	− 0.04
			Provera	− 0.11
			5-Trifluoromethyl-2'-deoxyuridine	− 0.52
			Yoshi-864	− 0.66
			Olivomycin	− 1.06
Lung	Tomizin	3.19	Streptozotocin	0.35
	Daunomycin	1.74	Chlorambucil	0.32
	1-Acetyl-2-picolinylhydrazine	1.09	Prednisone	0.32
	Cycloleucine	0.99	Thio-TEPA	0.29
	L-Asparaginase	0.71	Chromomycin A_3	0.29
	Dibromomannitol	0.60	Distron	0.26
	Platinum salt	0.60	Stilbestrol	0.25
	Testosterone	0.59	6-Thioguanine	0.24
	Ftorafur	0.44	Camptothecin	0.24
	Triethylenemelamine	0.42	Diiodobenzotepa	0.20
	17256E	0.41	6-Azauridine	0.11
	Dopan	0.38	5-Azacytidine	0.11
			Dactinomycin	0.10
			TIC-mustard	0.05
			Palphicerin	− 0.16
			Phenylalanine mustard	− 0.21
			5-Trifluoromethyl-2'-deoxyuridine	− 0.56
			Provera	− 0.61

TABLE 25.—*Ranking of compounds not clinically evaluated (continued)*

Tumor	Predicted active		Predicted inactive	
	Compound	$\hat{y}$-value	Compound	$\hat{y}$-value
Melanoma	5-Trifluoromethyl-2′-deoxyuridine	1.16	Prednisone	0.22
	Palphicerin	1.02	5-Azacytidine	0.21
	Porfiromycin	0.74	L-Asparaginase	0.19
	Iphosphamide	0.72	Dopan	0.17
	Ftorafur	0.52	Chromomycin A_3	0.08
	6-Thioguanine	0.50	Triethylenemelamine	0.07
	Distron	0.48	Myleran	0.06
	Thio-TEPA	0.45	Dibromomannitol	0.06
	Asaley	0.45	Cycloleucine	0.03
	Streptozotocin	0.44	Streptonigrin	0.03
	Diiodobenzotepa	0.40	Daunomycin	0.01
	Azotomycin	0.37	Stilbestrol	− 0.01
	Platinum salt	0.33	17256E	− 0.05
	ICRF-159	0.33	Testosterone	− 0.20
	Floxuridine	0.29	Provera	− 0.25
	6-Azauridine	0.26	1-Acetyl-2-picolinylhydrazine	− 0.43
			Tomizin	− 0.75

C: PATTERN-RECOGNITION METHOD: PRELIMINARY RESULTS

Rules for the prediction of clinical activity can be derived from a learning sequence based on table 1. The clinical evaluation S++ or S+ found in this table will place the corresponding compound in the first class, and compounds with the evaluation S− will constitute the second class. From this learning sequence and the principles outlined in the preceding section, each classification rule can be specified in the form of a table. The predictive strength of the resulting tables can be estimated by the number of errors in the classification of the elements of the learning sequence; with fixed complexity, the fewer the number of errors in the classification of compounds in the learning sequence, the higher the quality of a classification rule.

Because a decrease in the number of errors of classification can be achieved by an increase in the complexity of the rule for classification, one must take into account the degree of complication of the rule. A more reliable way to evaluate the predictive strength of a determinant rule can be obtained with the help of a "jackknife" procedure, with which the number of classification errors made with the learning sequence more accurately describes the predictive strength of the rule.

This procedure consists of the following: From the learning sequence, composed of l elements, the first element is eliminated and the classification rule is constructed on the basis of the remaining $l - 1$ elements. With the help of the constructed rule, a prediction is made as to which of the two classes the eliminated element belongs. The result of the prediction is compared with the true value. Then a second element is eliminated (the first is returned to the learning squence), a new determinant rule is similarly constructed, and the prediction is compared with the true value. This procedure is done l times (once for each element of the learning sequence). As a result, the number of elements for which the prediction did not coincide with the true classification is determined; this number characterizes the predictive strength of the rule.

A feature of the jackknife procedure is that a prediction is given each time about a new element of the classification rule, i.e., about an element not participating in the learning. Hence the number of errors made with the use of the jackknife will characterize the predictive strength of the rule more accurately than the overall number of errors of classification of the learning sequence.

The results of applying this method are shown in table 26 (breast, colon, and lung tumors, and melanoma), in which the classification rule and the number of classification errors of the learning sequence are presented. Note that not all compounds of the learning sequence for each tumor were classified correctly; e.g., 1 of the 13 clinically active compounds against lung tumor and 2 of the active compounds against melanoma were improperly categorized by the pattern recognition procedure.

To obtain an estimate of the predictive power of these classifications, we can refer to the number of errors made by the jackknife procedure (table 27).

Table 26 illustrates how the classification rules can be used to predict the clinical activity of compounds for which animal test results are known. The first column in this table gives the symbol for the independent variable representing average T/C values, the second identifies the corresponding animal tumor model, the third gives one or more intervals into which may fall the T/C value associated with a particular compound when tested against that model, and the fourth column displays the coefficient that applies to such a result. (The coefficient associated with a T/C value not falling in any given interval is assigned the value of 0.) One can classify the predicted

TABLE 26.—*Classification rules for clinical activity*

Tumor	Independent variable	Animal tumor model	Intervals	Coefficient k
Breast	x_1	L1210 ip	$205<x_1\leq 264$	10
			$x_1>264$	12
	x_2	L1210 sc	$x_2\leq 294$	26
			$294<x_2\leq 430$	20
	x_3	P388	$x_3\leq 131$	22
			$222<x_3\leq 245$	23
	x_4	B16	$x_4\leq 145$	26
			$x_4\geq 184$	20
	x_5	LL	$x_5\geq 117$	10

Predicted activity: $\Sigma k_i<79$

	$\Sigma k_i>79$	$\Sigma k_i<79$
S++, S+	0	18
S−	5	1

Tumor	Independent variable	Animal tumor model	Intervals	Coefficient k
Lung	x_1	L1210 ip	$20<x_1\leq 363$	8
	x_2	L1210 sc	$188<x_2\leq 292$	9
			$x_2\geq 293$	1
	x_3	P388	$x_3\leq 127$	30
			$x_3\geq 194$	21
	x_4	B16	$x_4\geq 163$	9
	x_5	LL	$100<x_5\leq 127$	28
			$x_5\geq 128$	22

Predicted activity: $\Sigma k_i>54$

	$\Sigma k_i<54$	$\Sigma k_i>54$
S++, S+	1	12
S−	14	4

Tumor	Independent variable	Animal tumor model	Intervals	Coefficient k
Colon	x_1	L1210 ip	$x_1\leq 146$	19
			$146<x_1\leq 363$	29
	x_2	L1210 sc	$154<x_2\leq 292$	10
			$x_2>292$	20
	x_3	P388	$x_3\leq 174$	11
			$174<x_3\leq 208$	20
	x_4	B16	$x_4\leq 117$	29
			$x_4\geq 126$	20
	x_5	LL	$106<x_5\leq 113$	29
			$x_5>113$	19

Predicted activity: $\Sigma k_i>80$

	$\Sigma k_i<80$	$\Sigma k_i>80$
S++, S+	1	10
S−	25	2

Tumor	Independent variable	Animal tumor model	Intervals	Coefficient k
Melanoma	x_1	L1210 ip	$x_1\leq 166$	19
			$x_1\geq 325$	14
	x_2	L1210 sc	$123<x_2\leq 327$	19
			$x_2>327$	14
	x_3	P388	$222<x_3\leq 290$	33
	x_4	B16	$x_4\leq 191$	11
			$191<x_4\leq 206$	22
	x_5	LL	$x_5\leq 100$	16
			$x_5\geq 113$	17

Predicted activity: $\Sigma k_i>82$

	$\Sigma k_i<82$	$\Sigma k_i>82$
S++, S+	2	5
S−	20	1

TABLE 27.—*Estimates of predictive power of classifications* [a]

Tumor	No. of false negatives	No. of false positives
Breast	1 (5.5)	2 (33.3)
Colon	1 (9.1)	9 (33.3)
Lung	3 (23.1)	3 (16.7)
Melanoma	2 (28.5)	4 (19.0)

[a] *Numbers in parentheses* are estimates of the probabilities of false-negative and false-positive prediction errors expressed as percentages.

activity of drugs by adding all coefficients determined by use of this table and noting whether the sum of coefficients is greater than the threshold value.

For example, to classify the predicted activity of Yoshi-864 against clinical breast tumors, we first obtain the following average T/C-values from table 19:

Independent variable	x_1	x_2	x_3	x_4	x_5
Tumor model	L1210 ip	L1210 sc	P388	B16	LL
Average T/C	310	150	291	189	113

With x_1 greater than 264, the corresponding coefficient (table 26) equals 12; similarly, the coefficients of $x_2, \ldots, x_5$ are 26, 0, 20, and 0, respectively. (The coefficients of x_3 and x_5 are 0 because the corresponding values of x do not fall in any of the intervals given in the third column of table 26.) The sum of these five coefficients is $12 + 26 + 0 + 20 + 0 = 58$. The threshold value for use with table 26 is 79; because 58 is less than 79, Yoshi-864 is predicted to be active against human breast tumors.

Classifications of predicted activity of other compounds for which sufficient animal test data are available but for which clinical activity has not been established are given in table 28 (breast, colon, and lung tumors, and melanoma).

D: SUMMARY

The applications of methods for ranking (classifying) compounds presented here should be regarded as preliminary. With regard to applications of the regression method, the clinical activity of more compounds against additional human tumors is required as well as responses of compounds when tested against new experimental sys-

TABLE 28.—*Classification of compounds with unknown clinical activity by pattern recognition methods*

Tumor	Evaluated as active compounds	Σk_i	Evaluated as inactive compounds	Σk_i
Breast	*cis*-Pt(II)	26	5-Trifluoromethyl-2′-deoxyuridine	84
	Dactinomycin	36	Provera	84
	TIC-mustard	42	DTIC	84
	Cycloleucine	48	6-Azauridine	84
	Olivomycin	49	Testosterone	84
	Porfiromycin	52	Triethylenemelamine	85
	Azotomycin	52		
	Procarbazine	52		
	Streptozotocin	52		
	Dibromomannitol	52		
	L-Asparaginase	52		
	Thio-TEPA	52		
	Streptonigrin	52		
	Daunomycin	56		
	Yoshi-864	58		
	Dopan	62		
	Distron	62		
	Chromomycin A_3	62		
	ICRF-159	62		
	6-Thioguanine	62		
	Mithramycin	62		
	Methylnitrosourea	62		
	Ara-C	68		
	Camptothecin	72		
	1-Acetyl-2-picolinylhydrazine	74		
	Myleran	74		
	Stilbestrol	74		
	Prednisone	74		
	17256E	74		
	Trimethylcolchicinic acid methyl ether	74		
	Palphicerin	75		
	Tomizin	78		
Colon	5-Trifluoromethyl-2′-deoxyuridine	98	Dibromomannitol	79
	Methylnitrosourea	89	Cycloleucine	79
	Myleran	88	Dopan	78
	Stilbestrol	88	Diiodobenzotepa	78
			Chromomycin A_3	78
			Daunomycin	78
			Yoshi-864	78
			Triethylenemelamine	78
			Mithramycin	78
			Provera	78
			6-Azauridine	78
			Tomizin	69
			Thio-TEPA	69
			Testosterone	69
			L-Asparaginase	59
			17256E	59
			Distron	58
			Olivomycin	49
			Prednisone	49
			Palphicerin	39

TABLE 28.—*Classification of compounds with unknown clinical activity by pattern recognition methods (continued)*

Tumor	Evaluated as active compounds	Σk_i	Evaluated as inactive compounds	Σk_i
Lung	Tomizin	67	Provera	52
	TIC-mustard	67	5-Trifluoromethyl-2′-deoxyuridine	52
	cis-Pt(II)	58	Dopan	49
	Dactinomycin	58	Diiodobenzotepa	49
	Prednisone	58	Distron	49
	17256E	58	Chromomycin A_3	49
	Testosterone	58	Palphicerin	49
	Stilbestrol	58	Triethylenemelamine	43
	Phenylalanine mustard	58	Daunomycin	37
	5-Azacytidine	57	1-Acetyl-2-picolinylhydrazine	30
			Camptothecin	30
			Ftorafur	28
			Streptozotocin	28
			Dibromomannitol	28
			6-Thioguanine	28
			Cycloleucine	28
			Chlorambucil	28
			6-Azauridine	28
			Thio-TEPA	28
			L-Asparaginase	0
Melanoma	Palphicerin	82	5-Azacytidine	80
			Triethylenemelamine	80
			Dopan	66
			Asaley	66
			Diiodobenzotepa	66
			5-Trifluoromethyl-2′-deoxyuridine	66
			cis-Pt(II)	66
			Cycloleucine	66
			Prednisone	66
			Floxuridine	66
			6-Azauridine	66
			Thio-TEPA	66
			L-Asparaginase	65
			Tomizin	58
			Daunomycin	55
			Porfiromycin	49
			Streptozotocin	49
			Ftorafur	47
			Distron	47
			Chromomycin A_3	47
			Iphosphamide	47
			6-Thioguanine	47
			Provera	47
			ICRF-159	47
			Testosterone	47
			1-Acetyl-2-picolinylhydrazine	46
			Azotomycin	30
			Dibromomannitol	30
			Myleran	30
			Stilbestrol	30
			17256E	30
			Streptonigrin	30

tems. Application of the more general pattern recognition method should be improved when additional information about the compounds is taken into account.

The initial applications of the two methods described here have resulted in differing predictions in a number of instances for compounds the clinical activity of which is unknown. These differences may largely disappear as the required data for more comprehensive applications become available, or it may become evident that one method establishes a clear-cut superiority in its accuracy of prediction in comparison to the other. Only through additional investigation will the answer to this question become known.

For the present, those compounds predicted by both methods to be active against a given human tumor might be regarded as constituting the highest priority group for clinical testing. Collaborative efforts to improve clinical prediction through increasing the quality and quantity of the data base are expected to resolve some of the present uncertainties and to enlarge the list of compounds and human tumors for which useful clinical predictions can be made.

Chapter V: Conclusion: Prospects for the Development of Methods for Studying the Antitumor Effects of New Substances[1]

With the development of chemotherapy, a number of types of malignant neoplasms can be treated successfully (*245, 248, 249, 328–330*).

Cancers for which chemotherapy has been effective so that patients were free of disease and achieved a normal life-span are listed in table 29 (*329*).

Obviously, the most frequently encountered forms of malignant tumors are not included. Nevertheless, with the availability of new drugs and the use of combinations of drugs and combined modalities, significant responses are being obtained for the common solid tumors (*245, 248, 249, 329, 331–334*).

Advanced cancers that may be considered responsive to chemotherapy, with elicitation of definitive increases in survival time are given in table 30 (*329*). An additional group (table 31) has been partially responsive to drugs, but data on survival time are still preliminary (*329*). Progress is being made in the treatment of other types of cancer including bladder, thyroid, and hepatocellular carcinoma.

It must be emphasized that investigators have been reasonably successful in the selection of antitumor agents and their studies have the potential for prediction of antitumor activity against specific forms of neoplasia. Whether candidate drugs possess a broad or narrow spectrum of action may be determined. Whether the spectrum and selectivity of antineoplastic action of analogs of known drugs have been altered in experimental tumor systems can also be shown. On the basis of experimental studies, we can project the characteristic features of the dynamics of tumor growth inhibition on exposure to the drugs. A tentative prediction can be provided of the effective dose range of drugs and of the optimal therapeutic schedule. In some instances and on the basis of tests in tumorous animals and in vitro, judgments can be made concerning pharmacokinetic characteristics and the mechanisms of action of antitumor substances. The use of special methods for studying the pharmacokinetics, metabolism, and the mechanisms of action allows us to predict the effects of drugs on tumors localized in specific areas in the host, and, in conjunction with toxicity studies, to project possible damage to one or another set of normal organs and tissues. Information is provided that may help in our optimizing the mode of therapy and in increasing the selectivity of antitumor effects of the drugs.

The current study has also permitted the examination of relationships between the efficacy of drugs in the treatment of specific types of human tumors and the biologic activity of these compounds. Elucidation of such relationships holds promise for the prediction of the effect of new drugs on the various types of human tumors. Generally, however, the problem of prediction of the spectrum of antitumor effect in clinical trial for most newly synthesized drugs on the basis of experimental data remains unresolved. As a corollary to this problem is the need to synthesize drugs which selectively suppress the growth of specific types of tumors.

One approach to its solution requires continuation of extensive investigation of qualitative and quantitative differences and similarities between normal and malignant cells on the one hand and between various human and animal tumors on the other.

In this regard, the studies being performed on the metabolic characteristics of human and animal tumors may be considered as being highly pertinent. They may aid not only in rational synthesis of new antitumor drugs but also in the rational selection of drugs for the treatment of specific types of tumors.

The characterization of the metabolic profile of tumor types constitutes a comprehensive program which includes elucidation of the total pattern of the biosynthetic pathways and their interrelationships, the reactions involved in catabolism, energy exchange, transport of materials to the cell, the systems involved in regulation of all of these processes, and the status of the endogenous pool of metabolites and coenzymes.

It appears impractical to study each tumor with respect to all the parameters mentioned above, and, in fact, this may not be necessary. Careful selection is essential if one is to study precisely those metabolic features which can serve as biochemical criteria for an indication of the susceptibility of a tumor to drugs of known or presumed mechanisms of action.

In this approach, careful consideration should be given to the fact that the metabolic pathways for a drug and the biologic targets it damages, i.e., enzymes, nucleic acids, membranes, etc., may be essentially the same in normal tissues and tumors. This can account for the degree of relative selectivity of the antitumor effects of drugs.

Also, when the drug is administered on appropriate therapeutic schedules, the cells of the normal tissues may repair their damage more readily than the cells of the

Abbreviations: CNS = central nervous system; 5-FU = 5-fluorouracil; ara-C = cytosine arabinoside; DTIC = dacarbazine; NCI = National Cancer Institute.

[1] This chapter was prepared by Abraham Goldin, Ira Kline, Zoya P. Sof'ina, and Anatoli B. Syrkin.

TABLE 29.—*Cancers for which drugs have been effective for some patients' achievement of a normal life-span*

Acute leukemia in children	Hodgkin's disease
Burkitt's lymphoma	Retinoblastoma
Choriocarcinoma	Skin cancer
Embryonal rhabdomyosarcoma	Testicular carcinoma
Ewing's sarcoma	Wilms' tumor
Histiocytic lymphoma	

sensitive tumors. Thus a fundamental problem consists of finding differences in the metabolism of tumors that will be sensitive to the administration of therapeutic doses of antitumor drugs. Extensive investigations have been conducted to characterize the biochemical determinants of sensitivity of tumors to antimetabolites, e.g., purine analogs, pyrimidines, and their nucleosides (*335–338*).

Some relationships have been found between the rates of lethal synthesis, the ratio of the rates of biosynthesis of purine and pyrimidine nucleotides de novo and the salvage pathways, the inhibition of the target enzyme under the influence of the active forms of the antimetabolites, and the sensitivity of the cells of different animal tumors. However, these criteria individually may not be wholly adequate for predicting the sensitivity of a tumor to an antimetabolite. It seems logical to assume that the sum total of the metabolic characteristics will allow this to be done with greater probability.

The efforts of researchers have been directed to the search for an integral index of tumor sensitivity to different drugs. One of the criteria of this type for the purine and pyrimidine analogs involves the dynamics of drug incorporation into the nucleic acids of tumor cells. In general, the analog may be incorporated into the nucleic acids of sensitive tumor cells more extensively and may be held there longer in comparison with cells of resistant tumors.

The causes of the death of tumor cells under the influence of antimetabolites may frequently involve not just a single metabolic block but several, each of them disturbing an entire chain of linked biosynthetic reactions. Inasmuch as consideration should also be given to the relationship between the cytotoxic effect of many antimetabolites and the phase of the cell cycle, it is clear that the interrelationships of drug and cellular response are highly complex and point to the potential usefulness of mathematical modeling methods.

In fact, the simplified models created in some laboratories that involve the action of the pyrimidine analogs (5-FU, ara-C) and antifolates on tumor cells do allow

TABLE 30.—*Cancers responsive to chemotherapy with improvement shown in patients' survival*

Adrenal cortical carcinoma	Malignant insulinoma
Adult acute leukemias	Multiple myeloma
Breast carcinoma	Neuroblastoma
Endometrial carcinoma	Ovarian carcinoma
Lymphocytic lymphomas	Prostate cancer

TABLE 31.—*Cancers responsive to chemotherapy for which clinical improvement in patients' survival is preliminary*

Cancer of the CNS	Malignant melanoma
Endocrine gland tumors	Oat cell carcinoma of the lung
Gastrointestinal cancer	Osteogenic sarcomas
Head and neck cancers	Soft tissue sarcomas
Malignant carcinoid tumors	

prediction of the dynamics of their death as a function of dose and time of exposure to the drug (*339–342*).

Recently, the methodologic approaches devised for predicting the effectiveness of antimetabolites in the treatment of animal tumors have begun to be transferred to the clinical realm. This transfer has been supplemented by improvement in the isolation and cultivation methods of human tumor cells, analysis of the nucleotide pool, and alteration of the pool under the influence of inhibitors (*343*).

Progress will undoubtedly be made in this area with the further development of the biochemical criteria pertaining to the susceptibility of various human tumors to antimetabolites.

As regards other classes of antitumor compounds, including alkylating agents, antibiotics, and substances of plant origin, a complete understanding of the underlying causes of sensitivity and resistance to them of human and animal tumors is lacking.

Primary targets for attack on the part of the alkylating agents are the DNA, RNA and nuclear protein molecules; thus one of the important characteristics of a tumor cell governing the extent of sensitivity is its ability to repair deficiencies in the structure of the alkylated DNA molecule and to eliminate the damaged RNA and protein molecules.

Evaluation of the level of the enzymes of DNA repair synthesis is important: the higher the level, the lower the sensitivity of the cell to the alkylating agents (*344, 345*).

The alkylation of the RNA molecules leads to the impairment of its processing and hence its functions in translation. The more rapidly the cell eliminates the damaged RNA, the more readily will unimpaired protein synthesis be restored. Data indicate that the alkylation of the RNA molecules per se may serve as a signal for the induction of synthesis of specific RNases, which selectively eliminate the damaged molecules (*153, 346*). A deficiency in this regulatory system may be the cause of the high sensitivity of cells to alkylating agents.

Some representatives of this class of antitumor compounds possess high affinity for the membrane of tumor cells and disturb active transport of substances as well as the energy functions of the membranes of the mitochondria and the endoplasmic reticulum.

The sensitivity of various tumors to such membranotropic drugs may depend in certain measure on the structural and functional intactness of their membranes (*347, 348*).

Finally, a group of alkylating agents become active cytostatics only after metabolic transformations under the influence of microsomal NADP-dependent hydroxylases.

They include cyclophosphamide, DTIC, and nitrosourea derivatives (*261, 349*). The sensitivity of tumors to these compounds depends on the level of this enzyme system.

Many antibiotics capable of intercalating between the bases of the double helix of DNA resemble alkylating agents in the mechanism of their cytotoxic effect. The search for biochemical criteria of tumor sensitivity to antibiotics of this class could follow the same lines as for alkylating compounds.

In addition, further development of methods of human tumor heterotransplantation and cultivation in vitro may provide substantial assistance in fundamental investigations and in the prediction of the spectrum of action of antitumor drugs.

Until recently, evaluation of drugs against human neoplasms was conducted primarily in cell culture, and the correlation between the sensitivity to drugs of the same tumors in vitro and in clinical trial has generally been low. Only solitary investigators have succeeded in obtaining a high proportion of coincidence of results. Despite the lack of success and the complexities arising in connection with this work, studies along this line are being continued. Several investigators have devised or reported improvements in cultivating procedures and techniques for evaluating the effects of such drugs (*350–356*).

Concurrently, as in the Division of Cancer Treatment at the NCI with its rational screening approach, scientists at other research centers have expressed great interest in the use of heterotransplantation of human tumors for 1) screening for new antitumor agents, 2) predictions of the spectrum of clinical activity, and 3) fundamental investigations of antitumor drug activity.

The growth of human tumors in animals depends on the suppression or exclusion of the immune response of the host, and this has been achieved by the injection of various immunosuppressants. However, the immunosuppressants may alter the host–tumor relationship and complicate interpretation of the results.

The development of methodology for cultivation of tumor tissues in diffusion chambers (*357–362*) and especially the availability of mutant athymic mice have made studies with xenografts of human tumors in these animals possible without additional conditioning of the mice. Although thymectomized mice that are then irradiated and have had their bone marrow reconstituted have been successfully used (*363–365*), the simplest method technically would appear to be that of heterotransplantation of tumors in athymic mice. Studies with such models have begun and provide a highly important feature of the new prospective screen being used at the Division of Cancer Treatment, NCI. Human tumors growing in athymic mice preserve most of their biologic, biochemical, and immunologic characteristics (*366–369*). Some tumors have been transplanted repeatedly, with the production of individual strains (*370*). After 3–4 passages, some tumors, which previously grew slowly, began to grow more rapidly, thereby allowing more efficient performance of chemotherapeutic experiments with them. Experience in this field is still limited, however. Of significance in relation to humans is the fact that tumors of the same type taken from different patients can show different sensitivity to antitumor drugs (*371, 372*).

Studies with xenografts of human tumors in athymic mice (as well as in diffusion chambers) represent an approach of great potential, and extensive investigations with these mice are surely warranted. Certain limitations may be noted in the utilization of the athymic mice, and their influences on tumor growth and chemotherapy should be investigated with a view to further improvement of the xenograft model. The mice are apparently not completely devoid of immune mechanisms which may alter tumor growth and drug responsiveness. The primary incidence of growth of certain tumor types is not high; generally, these do not metastasize readily. The vasculature of the tumor would appear to be that of the host. How the athymic mice could be used to identify new drugs that exert their antitumor effects via the immune system of the host is not clear. The necessity for maintaining germ-free conditions for their reproduction and maintenance is an obstacle to the widespread use of athymic mice. The effect on the sensitivity to drugs of accelerated tumor growth in the production of human tumor lines has not been clarified.

Clearly, research on the metabolism and pharmacokinetics of antitumor drugs should receive increased emphasis. Also, consideration should be given to the fact that the medicinal form in which the drug is administered may exert a substantial effect on its distribution, bioavailability, metabolism, and, consequently, on its antitumor activity. Thus a rational approach to the creation, utilization, and study of medicinal forms should receive additional serious attention.

From the above, it is evident that in any compilation of well-founded recommendations for the use of antitumor drugs and especially for prediction of their effect in patient therapy, the attainment and processing of a considerable quantity of information will undoubtedly be necessary and advantageous. The volume of data to be analyzed is so great that the analysis may best be performed by mathematical methods and computer devices. Mathematical methods will surely play an increasingly greater role in tumor chemotherapy, and it is projected that they will aid in the selection of the most useful information from the large data pool obtained by diverse methodologies. Mathematical modeling approaches will certainly facilitate and accelerate progress in the field of tumor chemotherapy.

Chapter IV of this Monograph represents an initial attempt by Americans and Soviet specialists at predicting the spectrum of antitumor action of drugs by various mathematical methods.

As a result of this study, judgments of a prognostic nature have been advanced with respect to numerous new compounds. Specific substances were recommended for testing in certain forms of tumors. The activities of a number of the drugs on each of the four forms of human tumors under investigation in this study were predicted by both mathematical methods, a finding that lends support to the probability of discovering an antitumor effect by these drugs against the tumors in question. Future re-

search will show to what extent the mathematical approaches used are rational. The study performed has also shown that further joint efforts in the field of mathematical prediction will undoubtedly assist in the resolution of the now existing uncertainties and improvement of the prediction of the clinical activity of drugs. Improved classification of the activity of the known antitumor agents against the various types of clinical neoplasia underlies and will aid in the refinement of these mathematical approaches.

A comparison of the extensive data in a wide range of systems obtained in the United States and USSR has shown that the pooled data can be considered as an integral whole. This is important because it is indicative of valid prospects for further joint American–Soviet research which will allow a significantly greater increment of representative material to be obtained for analysis.

The factual material cited in this Monograph is being made available to various specialists for examination and will undoubtedly be the subject of future studies. Results of experimental and clinical studies of the individual drugs presented may also be of special interest to chemotherapists.

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APPENDIXES I–IV

Results of Experimental Studies of Antitumor Drugs

APPENDIX I.—*Results of experimental studies in the United States with drugs developed here* [a]

NSC No.	Compound	Drug vehicle	Tumor	Site and inoculum	Expt. No.	Parameter of effect [b]	Controls	Treatment: Route	Treatment: Schedule, days	Doses, mg/kg/injection: Tested	Doses, mg/kg/injection: Optimal	Percent ILS or tumor inhibition	Survivors/total	Day of evaluation	ED50, μg/ml
26271	Cyclophosphamide	Saline	L1210	ip, 1×10^5	1562	MST	9.9	ip	5 only	350–84	172	224	2/8	60	
				" "	1711	"	9.0	"	" "	400–135	280	136	0/8	32	
				" "	1719	"	9.5	"	" "	400–86	140	124	"	60	
				" "	1740	"	8.9	"	" "	"	240	248	"	31	
				" "	6142	"	8.5	"	" "	400–150	300	148	0/10	60	
				ic, 1×10^5	232	"	8.2	"	1 only	300–200	"	31	"	45	
				" "	233	"	9.9	"	" "	"	"	39	"	"	
				" "	1930	"	7.4	"	" "	400–100	100	29	0/8	20	
				" "	1933	"	9.0	"	" "	"	400	30	"	21	
				" "	1947	"	8.9	"	" "	400–50	"	24	"	33	
				sc, 1×10^6	643	"	9.0	sc	5 only	500–108	300	177	"	36	
				" "	661	"	10.0	"	" "	"	500	155	"	33	
				" "	663	"	9.0	"	" "	"	300	144	"	38	
				" "	665	"	9.5	"	" "	"	180	121	"	30	
				" "	668	"	9.0	"	" "	300–65	"	105	"	35	
				iv, 1×10^7	C218	"	4.0	ip	2 only	250–100	250	230	0/10	45	
				" "	C228	"	4.3	"	" "	225–44	225	211	"	60	
				" "	C230	"	4.3	"	" "	"	"	295	0/8	"	
				" "	C297	"	5.6	"	" "	400–200	400	503	4/10	45	
				" "	C315	"	4.0	"	" "	"	"	507	1/10	60	
			P388	ip, 1×10^6	2214	"	11.6	"	1–9	100–6.3	25	157	4/6	30	
				" "	1944	"	12.0	"	"	64–4	64	87	0/10	45	
				" "	3424	"	10.8	"	"	100–6.3	50	168	2/6	30	
				" "	4209	"	9.9	"	"	400–25	25	200	1/6	"	
				" "	0001	"	12.0	"	"	200–50	50	150	5/7	"	
				iv, 1×10^7	0008	"	8.0	"	2 only	300–200	300	650	10/10	60	
				" 1×10^6	0009	"	10.0	"	" "	"	"	500	"	"	
			B16	ip, 1 : 10	0002	"	17.0	"	1–9	200–6.3	50	58	0/6	"	
				" " "	0018	"	23.0	"	"	100–25	"	26	"	"	
				" " "	0019	"	13.0	"	"	"	25	42	"	"	
				" " "	0164	"	17.4	"	"	100–6.3	"	37	0/10	"	
				" " "	0008	"	16.0	"	"	100–25	100	43	0/6	"	
				sc, 1 : 10	0036	"	26.0	"	"	"	25	55	"	"	
				" " "	0023	"	"	"	"	"	50	17	"	"	
				" " "	0026	"	"	"	"	"	100	28	1/6	"	
				" " "	0098	"	21.3	"	"	80–40	40	64	0/10	"	
				" " "	0035	"	23.0	"	"	100–25	25	39	0/6	"	
				ic, 1×10^5	0001	"	14.0	"	"	100–12.5	50	21	0/10	"	
				" "	0004	"	12.0	"	"	"	"	20	"	"	
				ic, 1 : 10	0008	"	"	"	"	"	"	33	"	"	
			LL	sc, 1 : 5	0017	"	35.0	"	8 only	300–75	300	71	5/8	"	
				" " "	0031	"	28.8	"	" "	400–25	200	59	0/10	"	
				" " "	0019	"	30.0	"	" "	300–75	300	45	1/10	"	
				" " "	0003	"	39.0	"	" "	300–108	108	25	0/8	52	

	LL	iv, 1×10^5	0003	"	21.7	"	1 only	300–60	200	176	3/8	60
		" " "	0023	"	21.0	"	" "	450–90	133	328	6/8	90
	S180	sc, tumor frag	0471	Tumor wt	688 mg	"	q 12 hr, 1–7	45–2.8	45	95	0/6	8
		" " "	0498	" "	1,032 "	"	" " " "	70–4.4	35	96	"	"
		" " "	2477	" "	958 "	"	" " " "	100–25	37.5	91	"	"
		" " "	2478	" "	1,049 "	"	" " " "	37.5–30	"	92	"	"
		" " "	2596	" "	963 "	"	" " " "	50–6.3	50	78	"	"
	Madison	im, 1×10^5 cells	0008	MST	30.0	"	1, 9	180–39	108	11	0/8	46
		" " "	0005	"	35.0	"	" "	300–65	180	10	"	66
		" " "	0004	"	23.0	"	1–9	25–3.1	12.5	30	0/6	45
		" " "	0003	"	24.4	"	"	100–12.5	"	27	0/10	60
	AK leuk (Spont)		003	"	16.5	"	1 only	200	200	72	4/52	61
			0073	"	16.5	"	" "	160	360	60	1/5	"
			0399	"	14.0	"	" "	200	200	110	3/33	"
			0406	"	"	"	" "	150	150	64	0/34	66
			0407	"	"	"	" "	100	100	78	"	61
	LPC-1	ip, ascitic fl 1×10^5	0001	"	29.0	sc	14–42	64–2	32	100	0/12	Death
		" " " "	0013	"	21.0	"	"	108–14	23	209	0/10	"
		" " " "	0021	"	22.0	"	"	"	"	202	"	"
		" " " "	0016	"	21.0	"	"	"	14	123	"	"
		" " " "	0023	"	19.0	"	"	65–8.4	23	113	0/12	"
	Epend	ic, tumor frag	0074	"	24.0	ip	q 4 days, 5, 9	200–50	100	75	1/7	30
		" " "	0008	"	19.0	"	" " " " "	400–50	200	44	0/6	"
	Ca-755	sc, tumor frag	1856	Tumor wt	1,356 mg	"	1–11	200–12.5	50	83	0/10	12
		" " "	1859	" "	1,533 "	"	"	50–6.3	"	82	"	"
		" " "	0058	" "	792 "	"	"	180–11	45	100	"	"
		" " "	0063	" "	697 "	"	"	45–2.8	"	"	"	"
		" " "	0338	" "	1,086 "	"	"	90–5.6	"	"	"	"
	C3H mam	sc, tumor frag	0012	MST	52.5	"	2–10	80–20	23	1	"	80
		" " "	0017	"	69.8	"	"	20	20	0		84
		" " "	0019	"	58.0	"	"	"	"	35	1/10	79
		" " "	0020	"	58.8	"	"	"	"	45	0/10	86
		" " "	0024	"	48.0	"	"	"	"	29	"	64
	Friend	sc, tumor frag	0026	Tumor wt	1,056 mg	"	1–11	50–62	50	100	"	12
CMC		" " "	0001	" "	1,404 "	"	"	50–25	"	98	"	"
		" " "	0008	" "	1,358 "	"	"	100–6.3	"	100	"	"
		" " "	0016	" "	672 "	"	"	50–25	"	93	"	"
		" " "	0019	" "	583 "	"	"	"	"	90	"	"
Saline	Gardner	ip, 1×10^6	0001	MST	10	"	1–10	180–11.3	45	200	0/6	Death
		" "	0002	"	"	"	"	"	11.3	100	"	"
		" "	0003	"	12	"	"	"	45	150	"	"
		" "	0056	"	13	"	"	50–6.3	25	26	"	"
	AK leuk	ip, spleen susp	0008	"	8	"	"	180–11.3	45	275	"	"
		" " "	0007	"	10	"	"	"	"	120	"	"
	P-1534 leuk	ip, 1 : 10	0003	"	10.3	"	"	"	22.5	77	"	"
		" " "	0004	"	10.5	"	"	"	"	67	"	"
		" " "	0013	"	11.5	"	"	22.5–2.9	"	32	"	"
	P329 RCS (Kelly)	ip, 1×10^6	0004	"	14.3	"	"	180–11.3	11.3	6	"	"

APPENDIX I.—*Results of experimental studies in the United States with drugs developed here* [a] *(Continued)*

NSC No.	Compound	Drug vehicle	Tumor	Site and inoculum	Expt. No.	Parameter of effect [b]	Controls	Treatment Route	Treatment Schedule, days	Doses, mg/kg injection Tested	Doses, mg/kg injection Optimal	Percent ILS or tumor inhibition	Survivors/ total	Day of evaluation	ED50, μg/ml
26271	Cyclophosphamide	Saline	P329	ip, 1×10^6	0005	MST	14.4	ip	1–10	180–11.3	11.3	21	0/6	Death	
			RCS	" 1 : 6	0003	"	22.6	"	10–19	"	45	26	"	"	
				" "	0004	"	24.1	"	"	"	"	7	"	"	
				" "	0005	"	20.3	"	"	"	"	51	"	"	
				" "	0006	"	23.3	"	"	"	"	30	"	"	
			Ca-1025	sc, tumor frag	0005	Tumor wt	1,388 mg	"	1–10	40–5	10	100	0/10	15	
				" " "	0010	" "	1,628 "	"	"	"	40	"	"	"	
			P288	ip, 1×10^6	0002	MST	7.6	"	"	180–11.3	22.5	103	0/6	Death	
			leuk	" "	0003	"	11.2	"	"	"	90	58	"	"	
				" "	0004	"	9.2	"	"	"	45	98	"	"	
				" "	0001	"	8.8	"	"	"	"	186	"	"	
			P335	ip, 1×10^6	0005	"	6.7	"	1–death	200–12.5	25	201	"	"	
			leuk	" "	0003	"	7.2	"	" "	"	50	205	"	"	
				" "	0004	"	7.0	"	" "	100–12.5	"	71	"	"	
				" "	0005	"	6.9	"	" "	50–6.3	25	207	"	"	
				" "	0027	"	10.1	"	" "	100–12.5	"	96	"	"	
			P-1798	sc, 1×10^6	0006	"	28.0	"	1 only	200–12.5	200	29	1/10	60	
			lymphoma	" "	0008	"	31.8	"	" "	400–25	"	7	0/10	51	
			P-1081	ip, 1×10^6	0001	"	10.0	"	1–10	180–11.3	22.5	20	0/6	Death	
			chloro-	" "	0002	"	"	"	"	"	11.3	17	"	"	
			roleuk	" "	0003	"	9.7	"	"	"	45	28	"	"	
				" "	0004	"	9.5	"	"	"	"	45	"	"	
			S91	sc, 1 : 2	0001	Tumor wt	817 mg	"	1–11	100–25	50	100	0/10	21	
			mela-	" " "	0011	" "	792 "	"	"	50–12.5	"	88	"	"	
			noma	" " "	0043	" "	693 "	"	"	15–10	15	100	"	"	
				" " "	0044	" "	697 "	"	"	"	10	80	"	"	
				" " "	0045	" "	912 "	"	"	"	15	84	"	"	
			KB		E446										1,200
					E444										10
409962	1,3-Bis(2-chloroethyl)-1-nitrosourea	Saline	L1210	ip, 1×10^5	2295	MST	9.7	"	1 only	65–8.4	39	186	8/10	30	
				" "	2429	"	8.2	"	" "	60–15	30	208	5/8	"	
				" "	8643	"	9.4	"	1–9	16–2.0	8.0	146	2/6	"	
				" "	8644	"	8.8	"	"	"	4.0	129	0/6	"	
				" "	8651	"	9.6	"	"	"	8.0	110	1/6	"	
				" "	8666	"	"	"	"	4–2.0	2.0	193	2/6	"	
			L1210	ic, 1×10^6	0088	"	5.7	"	2 only	39–10	39	271	7/10	Death	
				" "	0099	"	6.5	"	" "	39–9.75	19.5	126	1/9	"	
				" "	0204	"	6.2	"	" "	62–3.7	31	146	0/10	45	
		Saline and alcohol	L1210	iv, 1×10^7	C408	"	4.5	"	" "	50–10	40	366	"	"	
				" "	C411	"	4.0	"	" "	"	"	225	"	60	
				" "	C437	"	4.2	"	" "	50–20	50	261	"	"	
				" "	0065	"	4.1	"	" "	60–10	60	587	3/10	"	

			L1210	sc, 1 × 10^6	0013	"	8.2	"	1–9	64–2.0	8.0	143	0/10	30	
				" "	0029	"	8.9	"	"	12–5.33	5.33	122	"	"	
				" "	0050	"	10.0	"	"	4.0–0.25	4.0	87	"	45	
		Saline	P388	ip, 1 × 10^6	5176	"	11.9	"	"	16–2.0	2.0	"	0/6	30	
				" "	5177	"	10.3	"	"	"	8.0	191	5/6	"	
				" "	5182	"	11.7	"	"	"	4.0	156	6/6	"	
				" "	5183	"	11.6	"	"	"	"	132	1/6	"	
		Saline and alcohol	P388	ic, 1 × 10^5	0003	"	10.0	"	1 only	50–10	30	90	1/10	60	
				" 1 × 10^6	0002	"	8.0	"	" "	"	40	143	0/10	"	
				" 1 × 10^5	0035	"	9.4	"	" "	50–30	"	102	2/10	"	
				iv, 1 × 10^7	0003	"	7.0	"	" "	50–10	"	757	5/10	"	
				" "	0004	"	10.0	"	" "	"	"	500	"	"	
		Saline	B16	ip, 1 : 10	0005	"	32	"	1–9	60–1.87	3.75	87	3/6	"	
				" " "	0007	"	22.5	"	"	"	7.5	95	0/6	"	
		Saline	B16	ip, 1 : 10	0018	"	15	"	"	30–3.75	7.5	113	0/10	"	
				" " "	0084	"	23	"	"	10–1.25	10	95	"	"	
		Saline and alcohol		sc, 1 : 10	0073	"	18	"	"	8–1.0	8	66	0/6	"	
		Saline		sc, 1 : 5	0069	"	23	"	"	8–0.5	4.0	84	0/10	"	
				ic, 1 × 10^5	0003	"	12	"	"	15–1.87	7.5	50	"	30	
				" "	0004	"	"	"	"	15–1.9	"	41	"	60	
				" "	0008	"	"	"	"	20–2.5	5.0	58	"	"	
		Klucel	LL	sc, 1 × 10^6	0105	"	23	"	1 only	160–5.0	80	117	4/10	"	
		Saline and alcohol		sc, 1 : 10	0156	"	22	"	" "	40–5.0	40	72	0/10	80	
		Saline and Tween 80		" " "	0139	"	28.4	"	" "	160–5.0	"	39	"	60	
		Saline and alcohol	AK leuk (Spont)		0431	"	14	"	" "	30	30	42	1/33	61	
					0432	"	"	"	" "	20	20	35	0/31	"	
		Saline	Epend	ic, tumor frag	0001	"	17	"	1–5	10–2.5	2.5	32	1/10	30	
				" " "	0003	"	20	"	"	10–1.25	5.0	50	6/6	"	
			S180	sc " "	3718	Tumor wt	1,549 mg	"	1–7	24–1.5	1.5	73	0/6	8	
				" " "	3728	" "	1,339 "	"	"	20–2.6	20	76	"	"	
			KB		B453										7
			KB		1233										1.2
79037	1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea	Klucel	L1210	ip, 1 × 10^5	8244	MST	9.2	"	5 only	200–6.3	50	179	1/6	30	
				" "	8245	"	10.3	"	" "	"	"	142	3/6	"	
		CMC		" "	2841	"	9.6	"	" "	800–6.3	"	136	2/6	Death	
				ic, 1 × 10^4	0010	"	8.4	"	1 only	288–18.0	36	177	6/10	"	
				" "	0011	"	8.8	"	" "	225–18.5	50	240	10/10	"	
		Klucel		iv, 1 × 10^7	C414	"	4.2	"	2 only	71–14	43	526	0/9	60	
				" "	C415	"	4.0	"	" "	"	28	775	3/10	"	

APPENDIX I.—*Results of experimental studies in the United States with drugs developed here* [a] *(Continued)*

NSC No.	Compound	Drug vehicle	Tumor	Site and inoculum	Expt. No.	Parameter of effect [b]	Controls	Treatment		Doses, mg/kg/injection		Percent ILS or tumor inhibition	Survivors/total	Day of evaluation	ED50, ug/ml
								Route	Schedule, days	Tested	Optimal				
79037	1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea	Klucel	L1210	iv, 1×10^7	C441	MST	4.4	ip	2 only	90–18	90	422	1/8	60	
		Saline		sc, 1×10^6	0034	"	8.3	"	1–9	24–10.7	16	240	1/10	45	
		and alcohol		" "	0043	"	9.3	"	"	8–0.5	8	134	0/10	"	
		Klucel	P388	ip, 1×10^6	4689	"	11.1	"	"	12.5–5.5	12.5	53	0/6	30	
				" "	4775	"	12.1	"	"	18–8.2	18	65	"	"	
				" "	4909	"	11.4	"	"	3.6–2.4	3.6	64	"	"	
				" "	0886	"	11.0	"	"	64–8.0	16	172	"	"	
				" "	0967	"	"	"	"	8–1.0	11.0	140	"	"	
				ic, 1×10^7	0001	"	6.0	"	1 only	71–15	29	400	3/10	60	
				" 1×10^6	0002	"	8.0	"	" "	"	43	650	6/10	"	
				" "	0003	"	10.0	"	" "	"	57	500	"	"	
				iv, 1×10^7	0003	"	7.0	"	" "	"	29	757	8/10	"	
				" 1×10^6	0004	"	10.0	"	" "	"	43	500	"	"	
		Saline	B16	ip, 1 : 10	0012	"	19.0	"	1–9	32–4	16	89	0/6	"	
				" " "	0027	"	21.0	"	"	"	"	185	3/6	"	
		Klucel		" " "	0014	"	17.0	"	"	"	"	150	1/6	"	
				" " "	0022	"	14.0	"	"	"	"	157	"	"	
		Saline		" " "	0003	"	25	"	"	"	4	38	0/6	"	
		Klucel		sc " "	0020	"	"	"	"	"	16	140	3/6	"	
				" " "	0053	"	26	"	"	"	"	130	2/6	"	
			B16	sc, 1 : 10	0026	"	26	"	"	"	26	23	0/6	"	
			LL	sc, tumor frag	0727	"	35.3	"	"	2–0.25	2.0	69	0/10	"	
				" " "	0735	"	32.7	"	"	"	"	07	"	"	
				im, 1×10^6	0277	"	24.8	"	1–11	64–4.0	8.0	–8	"	36	
		Saline and Tween 80		" "	0145	"	19.5	"	"	"	16	33	0/8	41	
		Saline and alcohol	LL	iv, 1×10^5	0009	"	19.7	"	1 only	60–12	60	26	"	60	
				" "	0012	"	25.3	"	" "	"	12	137	8/8	"	
		Klucel	AK leuk (Spont)		0461	"	14	"	" "	40	40	35	1/40	61	
					0467	"	"	"	" "	30	30	42	3/26	"	
			KB		0487										9.1
34462	Uracil mustard	Saline	L1210	ip, 1×10^5	0977	"	8.8	"	1–death	6.0–0.1	0.3	59	0/7	Death	
		CMC		" "	0933	"	8.5	"	"	12–1.5	1.5	41	0/6	"	
		Alkali and saline		" "	0454	"	8.6	"	"	3.7–1.2	3.7	30	"	"	

	Saline		" "	0548	"	10.2	"	" "	5.5–1.8	2.5	37	"	"
			" "	1479	"	8.3	"	" "	3.7–1.2	1.2	59	"	"
	CMC	L1210	ip, 1×10^4	0133	"	9.1	"	1–15	1.7–0.75	1.7	27	0/10	"
	Other [c]		sc, 1×10^6	0161	"	10.0	"	7–death	14–0.65	5.0	60	"	"
	Saline	P388	ip, 1×10^6	0065	"	11.0	"	1–10	6–0.38	0.75	200	3/6	"
		B16	ip, 1 : 10	0013	"	14.0	"	1–9	3.00–0.38	"	78	0/10	60
			" " "	0055	"	15.5	"	"	1.5–0.38	"	25	"	35
			" " "	0133	"	20.0	"	"	1.5–0.19	1.5	85	0/6	60
	Saline		" " "	0382	"	20.0	"	"	3.0–0.05	1.1	105	3/10	45
	and	LL	sc, tumor frag	0057	"	22.5	"	1 only	14–1.8	3.0	42	0/9	61
	Tween 80		im, 1×10^6	0251	"	24.0	"	1–11	1.0–0.13	0.25	10	0/8	50
	Other												
	CMC	Ca-755	sc, tumor frag	3009	Tumor wt	1,097 mg	"	"	1.69–0.68	1.69	73	0/10	12
			" " "	2905	" "	1,032 "	"	"	1.35–0.17	1.35	83	"	"
	Alkali and saline	S180	sc, tumor frag	0578	" "	838 "	"	1–14	12–1.5	1.5	79	0/6	8
	CMC		" " "	3106	" "	1,525 "	"	"	2.5–0.3	0.6	68	"	"
82196	TIC-mustard	CMC	L1210	ip, 1×10^5	1260	MST	8.2	"	1–9	200–25	100	208	0/8	Death
				" "	1332	"	10.1	"	"	180–39	108	167	"	"
		DMSO		" "	R099	"	8.9	"	"	240–20	80	135	"	30
		Other		" "	4623	"	8.2	"	"	87–21.8	87	139	0/10	45
		Saline		" "	4682	"	9.2	"	"	87–2.8	"	143	"	"
		and alcohol		sc, 1×10^6	0020	"	8.8	"	"	400–12.5	100	227	"	"
		Saline and Tween 80		" "	0034	"	8.3	"	"	150–66.7	66.7	201	"	"
		Other		ic, 1×10^4	0227	"	9.5	"	"	640–10.0	20	20	"	30
				" "	0228	"	9.2	"	"	"	40	55	"	"
				" "	0229	"	9.4	"	"	"	80	57	"	"
				" "	0230	"	"	"	"	"	"	27	"	"
				iv, 1×10^7	C414	"	4.2	"	2 only	265–53	212	183	"	60
				" "	C424	"	4.8	"	" "	371–27	371	250	"	"
				" "	C441	"	4.4	"	" "	600–120	600	313	0/9	"
				" "	C470	"	4.8	"	" "	693–137	462	325	1/10	"
		Saline	P388	ip, 1×10^6	0107	"	12.0	"	1–10	200–25	100	195	3/6	Death
		CMC		" "	0131	"	11.0	"	"	25–3.1	25	81	0/6	"
		Other		sc, 1×10^6	0001	"	19.2	"	1–9	200–25	100	55	6/10	30
		Water	B16	ip, 1 : 10	0005	"	19.0	"	"	150–10	19	26	0/6	60
		Klucel		" " "	0015	"	18.0	"	"	400–25	100	50	"	"
				" " "	0024	"	14.0	"	"	"	"	92	"	"
				" " "	0008	"	16.0	"	"	"	"	115	"	"
		Saline and Tween 80		sc, " "	0028	"	24.0	"	"	"	"	47	"	"

APPENDIX I.—*Results of experimental studies in the United States with drugs developed here* [a] *(Continued)*

NSC No.	Compound	Drug vehicle	Tumor	Site and inoculum	Expt. No.	Parameter of effect [b]	Controls	Treatment: Route	Treatment: Schedule, days	Doses, mg/kg injection: Tested	Doses, mg/kg injection: Optimal	Percent ILS or tumor inhibition	Survivors/ total	Day of evaluation	ED50, μg/ml
82196	TIC-mustard	Klucel	B16	sc, 1 : 10	0052	MST	29.0	ip	1–9	400–25	100	70	0/6	60	
				" " "	0025	"	27.0	"	"	200–12.5	200	25	"	"	
			LL	im, 1 × 10^6	0279	"	29.0	"	1–8	100–3.1	3.1	10	0/8	37	
		Saline and Tween 80		sc, 1 : 5	0018	"	32.0	"	8–16	400–25	50	23	1/10	60	
		Other		iv, 1 × 10^6	0023	"	16.3	"	7 only	405–180	405	72	0/10	55	
		Saline and Tween 80	Ependy	ic, tumor frag	0040	"	20.0	"	1–5	400–50	100	17	0/6	30	
		Klucel	Madison	im, 1 × 10^5	0012	"	35.4	"	1 only	800–100	200	13	0/8	62	
			AK leuk	ip, 1 : 10	0302	"	12.4	"	1–9	100–25	37.5	53	0/10	60	
		Saline		" " "	0002	"	20.0	"	"	50	50	35	"	45	
		Other	C3H mam	ip, tumor frag	0052	"	35.7	"	2, 9	249–73	73	51	"	56	
			KB		0543										4
					0797										18
85998	Streptozotocin	Saline	L1210	ip, 1 × 10^5	5165	"	9.8	"	1–9	200–12.5	100	55	0/6	30	
		Citric acid		" "	P041	"	8.8	"	"	"	50	38	"	50	
				" "	P042	"	"	"	"	"	100	50	"	30	
				" "	4658	"	8.7	"	"	150–67	67	48	0/10	45	
		Saline		ic, 1 × 10^4	0025	"	9.1	"	"	120–15	120	13	"	30	
		Other		sc, 1 × 10^6	0022	"	8.7	"	"	200–12.5	50	29	"	"	
		Water		" "	0023	"	8.5	"	"	"	100	40	"	"	
			P388	ip, "	0273	"	11.0	"	"	200–17.0	39	61	0/8	63	
		Other		" "	1659	"	10.9	"	"	200–12.5	50	71	0/10	30	
			B16	ip, 1 : 10	0626	"	19.4	"	"	75–33.3	"	34	"	60	
				" " "	0607	"	20.1	"	"	200–12.5	"	35	"	"	
				" " "	0075	"	23.0	"	"	160–20	40	23	"	"	
		Water	LL	sc, tumor frag	0003	"	29.0	"	8–16	"	20	15	0/8	52	
		Saline		im, 1 × 10^6	0156	"	21.0	"	1–11	200–12.5	200	21	"	48	
			Ependy	ic, tumor frag	0057	"	17.0	"	1–5	300–130	300	44	0/6	60	
				" " "	0116	"	15.2	"	"	800–50	100	150	"	"	
			KB	" " "	1506										100
13875	Hexamethylmelamine	Saline and Tween 80	L1210	ip, 1 × 10^5	2325	"	9.9	"	1–9	150–9.4	150	24	0/6	30	
				" "	2692	"	9.6	"	"	160–20	80	39	"	"	
				ic, 1 × 10^4	0067	"	7.3	"	1only	195–85	130	8	0/10	Death	
				sc, 1 × 10^6	0011	"	8.2	"	1–9	160–20	160	10	"	30	
		Saline and Tween 80	P388	ip, 1 × 10^6	3424	"	10.8	"	"	"	"	18	0/6	"	

		Klucel	B16	ip, 1 : 10	0382	"	18.7	"	1–18 (q 2 days)	400–25	200	24	0/10	60	
				sc, 1 : 5	0267	"	25.4	"	1–9	320–40	40	22	"	"	
			LL	sc, tumor susp	0727	"	35.3	"	"	400–12.5	50	68	"	"	
				" " "	0728	" "	28.4	"	1–18 (q 2 days)	"	25	93	4/10	"	
		CMC	Ca-755	sc, tumor frag	2726	Tumor wt	804 mg	"	1–11	294–36.8	80.4	94	0/10	12	
			S180	sc, " "	0094	"	457 "	"	1–7	280–83	125	86	0/6	8	
			KB		0799										31
					0799										100
19893	5-Fluoro-uracil	Water	L1210	ip, 1×10^5	1792	MST	9.2	"	1–9	32–2.0	16	73	0/8	75	
		Saline		" "	2137	"	8.4	"	"	65–9.0	23	102	"	30	
		CMC		ic, 1×10^4	0047	"	8.8	"	1 only	159–79.5	119.3	32	0/10	Death	
				" "	0041	"	8.7	"	" "	120	120	33	"	"	
		Water		iv, 1×10^7	C309	"	4.4	"	1–9	56–11	37.5	150	"	60	
		Saline	L1210	sc, 1×10^6	0031	"	8.9	"	"	96–6.0	24	39	"	40	
				" "	0035	"	8.3	"	"	36–13	"	55	"	30	
			P388	ip, 1×10^6	0178	"	11.2	"	"	65–8.0	23	105	0/8	"	
				" "	0269	"	11.3	"	"	60–7.5	15	112	1/8	46	
		Saline	P388	sc, 1×10^6	0001	"	19.0	"	3–7 (q 4 days)	400–50	100	26	0/3	30	
				iv, 1×10^6	0015	"	11.0	"	1–9	28–12	28	59	1/10	60	
			B16	ip, 1 : 10	0046	"	21.0	"	1–17	20–2.5	20	61	0/10	35	
				" " "	0066	"	19.5	"	"	40–5.0	"	69	"	60	
				sc, " "	0035	"	23.0	"	1–9	40–10	10	47	0/6	"	
		Klucel		" " "	0046	"	25.5	"	"	"	"	54	"	"	
		Saline	LL	sc, tumor frag	0012	"	31.0	"	8–16 (daily)	40–5	20	40	0/10	"	
		Klucel		" " "	0016	"	27.5	"	" " "	"	"	32	"	"	
		Saline		im, 1×10^6	0106	"	19.5	"	1–11	80–5	10	23	0/8	40	
				" "	0244	"	26.0	"	"	"	20	30	"	"	
			AK leuk	ip, 1 : 10	0233	"	17.0	"	1–5	80–1.3	30	61	0/10	60	
		CMC	Ca-755	sc, tumor frag	A180	Tumor wt	1,441 mg	"	1–11	40–10	10	93	"	12	
		Saline	Ependy	ic, " "	0002	MST	19.2	"	1–5	40–2.5	20	30	0/6	60	
		MC	S180	sc, " "	2523	Tumor wt	3,750 mg	"	1–7 (q 12 hr)	45–37.5	37.5	94	"	8	
				KB	0013										0.085
					0193										0.65
145668	Cyclo-cytidine	Saline	L1210	ip, 1×10^5	3429	MST	9.6	"	1–9	600–118	266	158	1/10	30	
				" "	2060	"	9.0	"	"	800–100	400	211	1/8	40	
		Water		" "	2069	"	9.5	"	"	"	"	168	2/8	60	
				" "	2265	"	10.0	"	"	500–39	300	160	1/8	"	
				sc, 1×10^6	0755	"	9.0	sc	5–13	"	"	138	0/6	30	
				" "	0760	"	"	"	"	833–108	"	150	0/8	33	
				" "	0762	"	"	"	"	500–39	"	138	"	31	
				" "	0770	"	10.0	"	"	800–50	400	100	"	35	
				ic, 1×10^5	0014	"	10.4	ip	1–9	833–180	500	511	4/8	64	
				" "	0017	"	9.3	"	"	800–100	400	254	3/8	37	
			P388	ip, 1×10^6	0175	"	11.1	"	5–13	500–39	300	136	0/8	62	
				" "	0105	"	11.4	"	"	"	500	121	"	"	
		Saline		sc, "	0004	"	16.0	"	"	400–50	400	87	0/6	45	

APPENDIX I.—*Results of experimental studies in the United States with drugs developed here* [a] *(Continued)*

NSC No.	Compound	Drug vehicle	Tumor	Site and inoculum	Expt. No.	Parameter of effect [b]	Controls	Treatment		Doses, mg/kg/injection		Percent ILS or tumor inhibition	Survivors/total	Day of evaluation	ED50, μg/ml
								Route	Schedule, days	Tested	Optimal				
145668	Cyclocytidine	Water	P388	sc, 1×10^6	0102	MST	20.4	ip	5–13	800–100	400	66	3/8	36	
				ic, "	0005	"	12.9	"	"	600–100	300	132	1/8	38	
		Saline, sonified	B16	ip, 1 : 10	0248	"	23	"	1–9	800–100	400	10	0/6	45	
		Saline and Tween 80	LL	sc, tumor frag	0118	"	26.6	"	"	640–80	640	35	0/8	60	
		Saline	Epend	ic, tumor frag	0079	"	27	"	1–5	1,600–200	400	11	0/6	"	
			KB		0952										< 1.0
102816	5-Azacytidine		L1210	ip, 1×10^5	4321	"	8.7	"	1–9	10–1.25	2.5	109	"	30	
				" "	8892	"	8.4	"	"	6–0.75	3.0	128	"	"	
				" "	8891	"	8.9	"	"	"	"	124	"	"	
				" "	5891	"	9.6	"	"	6.3–3.1	3.12	64	"	"	
			L1210	sc, 1×10^6	0660	"	9.0	sc	"	12–0.75	1.5	100	0/8	31	
				" "	0703	"	"	"	"	5.0–0.65	3.0	138	"	30	
				" "	0016	"	8.9	"	"	3.2–0.2	3.2	57	0/10	"	
				" "	0033	"	8.2	"	"	4.8–1.07	"	143	"	"	
			L1210	ic, 1×10^4	0048	"	8.3	ip	"	6–0.75	0.75	28	0/6	"	
				" "	0003	"	9.0	"	"	3–0.75	3.0	20	"	"	
				iv, 1×10^6	C492	"	6.1	"	"	6–2.0	4.0	129	0/10	60	
			P388	ip, 1×10^6	1517	"	10.0	"	"	19–0.9	1.9	135	0/6	30	
				" "	5768	"	11.3	"	"	6–0.75	3.0	127	"	"	
				" "	0888	"	11.0	"	"	"	"	145	"	"	
				" "	0967	"	"	"	"	1.5–0.19	1.5	95	"	"	
			P388	sc, 1×10^6	0002	"	19.2	"	"	4.0–0.5	4.0	55	3/9	"	
				ic, 1×10^3	0018	"	13.0	"	"	7.5–3.4	3.4	30	0/10	45	
				" "	0019	"	14.7	"	"	"	5.0	42	1/9	"	
			B16	ip, 1 : 10	0327	"	20.6	"	"	6.0–0.75	3.0	"	0/10	60	
				" " "	0024	"	14.0	"	"	"	"	60	0/6	"	
				" " "	0007	"	18.0	"	"	"	"	44	"	"	
				" " "	0232	"	15.0	"	"	"	"	40	"	45	
			B16	sc, tumor susp	0024	"	31.0	"	"	"	0.75	66	2/6	60	
				" " "	0039	"	21.0	"	"	"	1.5	33	0/6	"	
				" " "	0105	"	23.0	"	"	40.–0.5	4.0	27	0/10	"	
				sc, 1 : 10	0202	"	"	"	"	3.2–0.2	1.6	26	1/10	"	
			LL	im, 1×10^6	0251	"	24.0	"	1–11	1.5–0.1	0.75	12	0/8	50	
				" "	0289	"	27.3	"	"	3.2–0.2	1.6	31	1/10	60	
			AK leuk (Spont)		0839	"	18.0	"	1–9	0.9	0.9	44	0/30	69	
					0840	"	"	"	"	0.6	0.6	22	"	"	
			C3H mam	sc, tumor frag	0039	"	42	"	16–24	6.0–1.8	2.7	39	0/10	59	

				" " "	0066	"	50	"	"	1.5–0.44	0.44	12	"	62	
			L-5178Y	iv, 1×10^7	C490	"	8.7	"	3, 7, 11, 15	30–10	20	27	"	60	
119875	*cis*-Platinum(II) diamminedichloride	Saline	L1210	ip, 1×10^5	1442	"	9.5	"	1–9	2.5–0.3	1.3	44	"	Death	
		Other		" "	1445	"	9.1	"	"		"	87	"	"	
				" "	1470	"	9.8	"	"	2.0–0.3	1.0	40	"	"	
		Saline		sc, 1×10^6	0647	"	9.0	"	"	4.0–0.5	2.0	55	0/8	17	
				" "	0034	"	8.3	"	"	3.0–1.3	3.0	92	0/10	45	
			P388	ip, 1×10^6	0196	"	10.0	"	"	4.0–0.5	2.0	197	3/6	30	
				" "	0315	"	12.0	"	"	8.0–0.5	"	147	"	"	
				sc, 1×10^6	0104	"	18.3	"	"	6.4–0.4	0.8	42	2/10	"	
			B16	ip, 1 : 10	0053	"	15.0	"	"	2.0–0.5	1.0	56	0/10	60	
				" " "	0056	"	17.0	"	"	"	2.0	129	"	"	
				" " "	0008	"	16.0	"	"	4.8–0.6	1.2	78	0/6	"	
				" " "	0029	"	17.0	"	"	2.0–0.5	2.0	88	0/10	"	
		Saline and Tween 80		sc, 1 : 10	0032	"	27.0	"	"	4.8–0.6	1.2	42	0/6	"	
		Saline		" " "	0024	"	31.0	"	"	"	"	25	"	"	
		Klucel		" " "	0035	"	23.0	"	"	"	"	54	"	"	
		Saline		" " "	0094	"	"	"	"	2.0–0.5	2.0	32	0/10	"	
		Saline and Tween 80	LL	sc, 1 : 5	0020	"	24.0	"	8–16	4.8–0.6	1.2	43	"	"	
		Klucel		sc, 1 : 5	0016	"	27.5	"	"	4.8–0.6	0.6	23	0/10	"	
		Saline and Tween 80	AK leuk (Spont)		0795	"	18.0	"	1 only	10.0	10.0	63	3/31	61	
			C3H mam	sc, tumor frag	0050	"	45.3	"	2, 7	6.0–1.8	1.8	24	0/10	57	
		Klucel	Epend	ic, " "	0057	"	17.0	"	1–5	3.0–1.3	1.3	61	0/6	60	
			KB		1501										0.018
					0798										1.8
15200	Gallium nitrate	Saline	L1210	ip, 1×10^5	8645	"	10.1	"	**1–9**	100–12.5	50	15	"	30	
				" "	8646	"	8.3	"	"	"	12.5	18	"	"	
				sc, "	0005	"	10.7	"	"	160–20	80	24	1/10	"	
			P388	ip, 1×10^6	2871	"	11.6	"	"	100–12.5	11.6	37	0/6	"	
				" "	5257	"	9.4	"	"	"	9.4	30	"	"	
				sc, "	0001	"	19.2	"	"	160–20	19.2	−1	0/10	"	
			B16	ip, 1 : 10	0152	"	21.0	"	"	400–50	50	2	0/6	60	
			LL	im, 1×10^6	0075	"	23.5	"	1–11	25–3.1	12.5	6	0/8	49	
			AK leuk	ip, 1 : 10	0046	"	18.0	"	9–17	50–12.5	50	5	0/10	60	
					0081	"	15.0	"	"	200–50	"	13	"	"	
			Epend	ic, tumor frag	0031	"	19.0	"	1–5	320–40	80	34	0/6	30	
				" " "	0066	"	17.5	"	"	120–50	50	17	"	60	
			KB		0800										72

APPENDIX I.—*Results of experimental studies in the United States with drugs developed here* [a] *(Continued)*

NSC No.	Compound	Drug vehicle	Tumor	Site and inoculum	Expt. No.	Parameter of effect [b]	Controls	Treatment: Route	Treatment: Schedule, days	Doses, mg/kg injection: Tested	Doses, mg/kg injection: Optimal	Percent ILS or tumor inhibition	Survivors/ total	Day of evaluation	ED50, μg/ml
1895	Guanazole	Saline	L1210	ip, 1×10^5	C443	MST	10.8	ip	1, 5, 9 (q 3 hr)	810–162	540	365	7/10	60	
				" "	C471	"	7.6	"	"	1,350–180	600	226	1/10	"	
		Water	L1210	sc, 1×10^6	0649	"	9.0	sc	"	833–180	500	66	0/8	23	
		Saline		ic, 1×10^5	0172	"	7.8	ip	"	500–100	"	28	0/10	45	
				" "	0174	"	10.4	"	"	"	"	9	"	"	
				iv, 1×10^4	0057	"	8.3	"	"	"	"	115	"	"	
				" "	0055	"	5.6	"	"	"	"	157	"	"	
		Saline, sonified	P388	ip, 1×10^6	0970	"	13.0	"	1–9	3,200–400	800	38	0/6	20	
		Saline and Tween 80		" "	0888	"	11.0	"	"	800–100	"	63	"	30	
		Water	LL	im, 1×10^6	0231	"	25.0	"	"	1,500–375	1,500	26	0/8	47	
				" "	0124	"	21.0	"	"	3,000–750	750	35	1/8	"	
		Saline		sc, tumor frag	0005	"	27.0	"	8–16	800–100	800	54	0/10	60	
				" " "	0016	"	27.5	"	"	"	400	30	"	"	
			Epend	ic, tumor susp	0148	"	20.1	"	1, 5, 9 (q 3 hr)	250–15.6	125	27	0/6	"	
			C3H mam	ip, tumor frag	0062	"	49	"	9–21 (q 3 hr)	810–238	238	26	0/10	63	
			AK leuk	ip, 1 : 10	0278	"	23	"	1–9	550–375	550	160	5/10	60	
		Water	Madison	im, 1×10^5	0021	"	36.8	"	"	1,000–125	500	23	0/8	57	
				" "	0025	"	32	"	"	600–300	400	32	"	59	
			KB		0799										51
71795	Ellipticine	Other	L1210	ip, 1×10^5	0007	"	9.2	"	"	128–4.0	32	126	2/10	30	
				" "	1691	"	8.8	"	"	64–8.0	16	102	0/10	23	
		Steroid susp		sc, 1×10^6	0648	"	9.0	"	1, 5, 9 (q 3 hr)	40–5.0	40	50	0/8	55	
		Saline and Tween 80	P388	ip, 1×10^6	0887	"	11.0	"	1–9	100–12.5	25	104	0/6	30	
				" "	0967	"	"	"	"	12.5–1.6	12.5	95	"	"	
				sc, "	0001	"	19.2	"	"	32–4.0	32	8	0/10	"	
		Saline	B16	ip, 1 : 10	0105	"	22.0	"	"	10–1.3	10	36	0/6	60	
				" " "	0098	"	20.0	"	"	80–10	40	47	"	"	

		Saline and Tween 80		sc	0105	"	23.0	"	"	32–4.0	16	20	0/10	"	
		Water	LL	im, 1×10^6	0251	"	24.0	"	"	12.5–1.6	6.3	8	0/8	50	
		Other	Madison	im, 1×10^5	0034	"	33.0	"	"	32–2.0	4.0	21	"	57	
		Klucel	AK leuk	ip, 1 : 10	0023	"	13.0	"	1, 5, 9	200–25	50	53	0/10	60	
		Saline		" " "	0023	"	22.0	"	" " "	75–18.8	37.5	38	"	45	
			Epend	ic, tumor frag	0039	"	20.0	"	1–5	64–8.0	32	22	0/6	30	
		Other		" " "	0128	"	25.5	"	"	640–2.5	80	24	"	60	
			KB		1068										2.3
					0802										0.34
83265	3-Trityl-thio-L-alanine	Other	L1210	ip, 1×10^5	1295	"	9.7	"	1–9	140–17	70	55	0/8	Death	
		Saline and Tween 80		" "	5438	"	9.3	"	1–9	100–12.5	50	75	0/10	30	
		Saline		sc, 1×10^6	0694	"	14.0	sc	q4hr q 2days (5–13)	65–5.0	23	50	1/8	45	
		Saline and Tween 80	P388	ip, 1×10^6	0888	"	11.0	ip	1–9	200–12.5	50	118	0/6	30	
		Water		" "	2715	"	"	"	"	90–8.0	40	86	0/10	"	
		Klucel		sc, 1×10^6	0001	"	19.2	"	"	120–15	60	40	1/8	"	
		Saline	B16	ip, 1 : 10	0098	"	20.0	"	"	200–25	50	50	0/6	60	
				" " "	0105	"	22.0	"	"	25–3.1	25	25	"	"	
		Klucel		sc," "	0105	"	23.0	"	"	120–15	15	17	0/8	"	
		Saline	LL	im, 1×10^6	0147	"	25.0	"	1–11	200–12.5	25	18	"	40	
			AK leuk	ip, 1 : 10	0078	"	24.0	"	1–9	10–2.5	10	37	0/10	60	
		Klucel		" " "	0136	"	17.0	"	"	80–1.2	2.5	35	"	"	
		Saline	Epend	ic, tumor frag	0059	"	21.5	"	1–5	75–25	75	18	0/6	"	
			KB		0340										1.0
					0349										42
118994	Inosine diglycolaldehyde	Saline	L1210	ip, 1×10^5	4302	"	9.3	"	1–9	280–35	70	88	2/6	30	
				" "	5221	"	8.6	"	"	200–50	200	187	"	"	
		Saline and Tween 80		" "	0005	"	10.7	"	"	400–50	"	75	0/8	"	
		Saline	P388	ip, 1×10^6	0700	"	11.0	"	1–10	300–37.5	150	109	0/6	"	
		Saline and Tween 80		sc, 1×10^6	0002	"	19.2	"	1–9	400–50	200	13	0/10	"	
		Saline	LL	im, 1×10^6	0114	"	28.5	"	1–11	300–39	65	15	0/8	60	
				' "	0089	"	23.0	"	"	300–37.5	23	43	"	49	
			AK leuk	ip, 1 : 10	0078	"	24.0	"	1–9	25–6.3	25	54	0/10	60	

APPENDIX I.—*Results of experimental studies in the United States with drugs developed here* [a] *(Continued)*

NSC No.	Compound	Drug vehicle	Tumor	Site and inoculum	Expt. No.	Parameter of effect [b]	Controls	Treatment		Doses, mg/kg/injection		Percent ILS or tumor inhibition	Survivors/total	Day of evaluation	ED50, μg/ml
								Route	Schedule, days	Tested	Optimal				
118994	Inosine diglycolaldehyde	Saline	AK leuk	ip, 1 : 10	0125	MST	19.0	ip	1–9	50–12.5	25	113	0/10	60	
			Ependy	ic, tumor frag	0045	"	20.0	"	1–5	480–60	120	2	0/6	30	
			KB		1397										> 100
126771	Dichloroallyl lawsone	Water	L1210	ip, 1×10^5	1747	"	13.7	"	1–9	75–6.2	25	4	0/10	99	
				" "	1660	"	9.0	"	"	50–12.5	50	13	0/6	35	
			P388	ip, 1×10^6	0301	"	10.0	"	"	50–10.0	10	20	"	"	
		Saline	B16	ip, 1 : 10	0017	"	16.0	"	"	100–12.5	100	12	"	60	
		Klucel		" " "	0007	"	18.0	"	"	"	50	8	"	"	
				sc, 1 : 10	0024	"	31.0	"	"	"	12.5	4	1/6	"	
				" " "	0035	"	23	"	"	"	50	36	0/6	"	
			LL	sc, tumor frag	0008	"	24.0	"	8–16	"	"	10	0/10	"	
				" " "	0012	"	31.0	"	"	"	100	11	"	"	
			KB		0797										1.8
132319	Indicine-*N*-oxide	Water	L1210	ip, 1×10^5	1682	"	9.1	"	1–9	200–6.2	200	35	0/6	35	
				" "	1706	"	8.7	"	"	800–400	600	47	"	"	
		Saline		sc, "	0005	"	10.7	"	"	800–100	800	12	0/8	30	
		Water	P388	ip, 1×10^6	3348	"	12.0	"	"	800–50	400	104	0/6	"	
		Water	P388	ip, 1×10^6	3621	"	9.0	"	"	"	200	111	0/10	"	
		Saline		sc, "	0002	"	19.2	"	"	800–100	800	23	"	"	
		Water	B16	ip, 1 : 10	0053	"	22.7	"	"	1,024–64	512	64	"	60	
				" " "	0055	"	24.8	"	"	"	"	57	"	"	
				sc, " "	0008	"	25.8	"	"	800–25	200	50	"	"	
				" 1 : 5	0267	"	25.4	"	"	"	400	31	"	"	
			LL	im, 1×10^6	0160	"	17.0	"	"	400–50	"	23	0/8	49	
		Saline		" "	0252	"	26.0	"	1–11	1,600–200	"	1	"	47	
			KB		1506										> 100
154890	Coralyne sulfoacetate		L1210	ip, 1×10^5	2695	"	9.5	"	1–9	160–5.0	160	36	0/6	30	
				" "	3189	"	10.5	"	"	128–8.0	128	64	0/10	60	
			P388	ip, 1×10^6	0069	"	10.0	"	"	600–5.0	160	125	0/6	30	
				" "	1217	"	12.0	"	"	150–9.3	75	83	0/10	"	
				sc, "	0002	"	10.3	"	"	160–20	160	35	"	"	
		Other	B16	ip, 1 : 10	0136	"	15.2	"	"	250–8.0	16	23	"	60	
		Water		" " "	0608	"	19.6	"	"	256–16	64	25	"	"	
				sc, " "	0004	"	27.8	"	"	256–8.0	8.0	33	"	"	
		Saline and Tween 80		" " "	0077	"	28.0	"	"	200–12.5	100	42	0/8	"	
			LL	sc, tumor frag	0052	"	20.5	"	"	200–6.3	12.5	53	0/10	"	

			" " "	0088	"	21.4	"	"	256–8.0	32	50	"	"	
			KB	1152										65
71851	α-Deoxy-thio-guanosine	Saline	L1210	ip, 1×10^5	2183	"	7.8	"	1–3	160–10	40	78	"	35
				sc, 1×10^6	0784	"	9.1	sc	5–13 (q 2 days)	600–75	600	58	0/8	30
		Saline and Tween 80	P388	ip, 1×10^6	0991	"	12.0	ip	1–9	50–12.5	50	62	3/6	20
		Saline, sonified	P388	ip, 1×10^6	1234	"	11.0	"	"	25–6.3	25	68	0/6	"
		Saline and Tween 80	LL	im, 1×10^6	0184	"	20.5	"	1–11	50–1.6	"	12	0/8	50
		Saline and Tween 80	AK leuk	ip, 1 : 10	0051	"	23.0	"	5, 9, 13	400–100	200	30	0/10	60
		Saline		" " "	0193	"	18.0	"	" " "	600–50	400	36	"	"
			KB		0376									0.65
126849	3-Deazauri-dine		L1210	ip, 1×10^5	4759	"	9.1	"	1–9	400–100	200	50	0/6	30
				" "	4025	"	9.6	"	"	300–132	"	51	"	"
				KB	1232									120
137679	6-Seleno-guanosine	Saline	L1210	ip, 1×10^5	5891	"	"	"	"	50–12.5	25	129	"	30
		DMSO		" "	P250	"	8.0	"	"	64–1.0	4	100	0/10	60
		Saline	P388	ip, 1×10^6	3332	"	10.5	"	"	"	16	98	0/6	30
				" "	1448	"	13.0	"	"	"	"	38	"	"
			B16	ip, 1 : 10	0715	"	21.3	"	"	"	1.0	36	0/10	50
				" " "	0176	"	"	"	"	"	16	30	"	60
				sc, " "	0029	"	30.3	"	"	"	"	51	"	"
				" " "	0102	"	32.0	"	"	"	32	31	"	"
			LL	sc, tumor frag	0111	"	23.0	"	"	"	23	65	"	"
			Gardner	ip, 1×10^6	0004	"	16.6	"	"	32–1.0	2.0	259	5/10	"
154020	Townsend's nucleo-side de-rivative	Saline	L1210	ip, 1×10^5	6124	"	8.5	"	"	50–12.5	25	74	0/6	30
				" "	3151	"	9.2	"	"	30–15	15	115	2/6	"
				sc, 1×10^6	0792	"	9.9	"	5–13	100–3.1	25	11	0/10	21
		Klucel	P388	ip, 1×10^6	3183	"	12.7	"	1–9	2.0–0.3	2.0	10	"	30
		Saline	LL	sc, tumor frag	0033	"	30.6	"	8–16	100–3.1	12.5	3	"	60
			KB		1152									79
169780	ICRF–187	Saline	L1210	ip, 1×10^5	0007	"	9.1	"	1, 5, 9	1,024–64	1,024	86	"	"
				" "	0011	"	9.3	sc	" " "	"	"	136	1/10	"

APPENDIX I.—*Results of experimental studies in the United States with drugs developed here* [a] *(Continued)*

NSC No.	Compound	Drug vehicle	Tumor	Site and inoculum	Expt. No.	Parameter of effect [b]	Controls	Treatment: Route	Treatment: Schedule, days	Doses, mg/kg injection: Tested	Doses, mg/kg injection: Optimal	Percent ILS or tumor inhibition	Survivors/ total	Day of evaluation	ED50, μg/ml
169780	ICRF–187	Water	L1210	sc, 1×10^6	0061	MST	9.1	ip	5–13	512–16	128	50	0/10	30	
				ic, 1×10^5	0013	"	9.4	"	1–9	256–16	256	46	"	31	
				" "	0015	"	9.7	"	"	512–32	64	32	"	36	
			B16	ip, 1 : 10	0116	"	20.0	"	1, 5, 9	800–25	800	"	"	60	
				" " "	0269	"	22.3	"	" " "	"	400	22.3	"	"	
		Klucel	B16	sc," "	0003	"	23.8	"	1–9	64–8.0	64	84	"	"	
				" 1 : 5	0181	"	22.0	"	"	"	"	68	"	"	
		Saline and Tween 80	Epend	ic, tumor frag	0179	"	20.3	"	1–5	256–8.0	256	42	0/6	"	
		Water	LL	sc, " "	0062	"	32.4	"	1, 5, 9	800–25	100	50	0/10	"	
			KB		1152										> 100
172112	Spirohydantoin mustard	Saline	L1210	ip, 1×10^5	6751	"	9.4	"	" " "	35–16	35	31	0/6	30	
				" "	3536	"	9.3	"	" " "	"	"	37	"	"	
			P388	ip, 1×10^6	4328	"	10.2	"	1–9	25–0.39	6.3	191	3/6	"	
				" "	3354	"	10.3	"	"	24–1.5	12	140	0/1	"	
		Saline and Tween 80		ic, "	0017	"	8.9	"	"	"	"	35	0/6	"	
				" "	0018	"	10.2	"	"	"	"	34	"	"	
		Saline	B16	ip, 1 : 10	0272	"	22.1	"	"	12.5–0.78	6.3	76	0/10	60	
				" " "	0271	"	17.1	"	"	"	0.78	163	2/10	"	
		Saline and Tween 80		ic, 1×10^5	0022	"	7.2	"	"	24–1.5	6.0	52	0/10	40	
		Saline	Epend	ic, tumor frag	0144	"	22.1	"	1–5	25–0.78	12.5	171	5/6	60	
				" " "	0143	"	23.4	"	"	"	"	156	6/6	"	
			LL	sc, " "	0007	"	23.9	"	1–9	25–1.6	3.1	14	0/6	"	
		Klucel		" " "	0112	"	20.3	"	"	24–1.5	6.0	41	0/10	"	
176319	Cain's quinolinium derivative	Saline	L1210	ip, 1×10^5	2499	"	9.8	"	1, 5, 9	75–12.5	25	201	3/6	30	
		Saline and Tween 80		" "	2453	"	9.4	"	" " "	50–12.5	25	169	"	"	
		Klucel		ic, "	0008	"	8.0	"	1–9	16–0.5	16	30	0/10	"	
			P388	ip, 1×10^6	2116	"	12.3	"	"	"	8.0	144	6/6	"	
				" "	1144	"	12.0	"	"	16–1.0	"	150	9/10	"	
		Klucel	B16	ip, 1 : 10	0145	"	16.9	"	"	16–0.5	"	24	0/10	60	
				" " "	0226	"	15.4	"	"	32–1.0	"	23	"	"	

				sc, 1 : 5	0155	"	24.5	"	"	16–0.5	1.0	11	"	30	
			LL	" " "	0024	"	31.9	"	8–16	"	2.0	12	"	60	
			KB		1439										9.5
178248	Chlorozotocin	Saline	L1210	ip, 1×10^5	5680	"	9.0	"	1 only	45–4.0	30	517	9/10	60	
		CMC	L1210	ip, 1×10^6	5828	"	8.1	"	" "	45–9.0	"	548	8/10	"	
		Water		ic, 1×10^5	0033	"	7.5	"	" "	64–4.0	16	20	0/6	30	
		Saline		" "	0222	"	7.9	"	" "	45–9.0	30	"	0/10	60	
				iv, 1×10^6	0001	"	5.6	"	3 only	60–7.5	"	133	"	"	
		Saline	P388	ip, 1×10^6	1245	"	12.6	"	1 only	67–13.0	13.0	138	5/6	30	
				" "	3335	"	11.8	"	" "	"	45.0	154	9/10	"	
			B16	ip, 1 : 10	0705	"	18.5	"	1–9	30–1.9	7.5	141	4/10	45	
				" " "	0158	"	20.8	"	"	6.7–1.3	6.7	187	6/10	60	
				sc," "	0095	"	19.4	"	1 only	67–13	30	43	0/10	"	
				ic," "	0021	"	12.3	"	1–9	30–1.9	7.5	46	0/8	30	
		Klucel	LL	sc, 1×10^6	0105	"	23.0	"	1 only	160–10	10	30	0/10	60	
		Saline		" "	0011	"	31.3	"	" "	67–13	45	45	"	"	
			Epend	ic, tumor frag	0144	"	22.1	"	1–5	20–1.3	5.0	170	3/6	"	
				" " "	0151	"	11.3	"	"	"	1.3	103	0/6	"	
			KB		0955										45
249992	Cain's acridine derivative	Clinical form	P388	ip, 1×10^6	0054	"	10.4	"	1, 5, 9	16.7–3.6	10.0	148	0/8	60	
				" "	2412	"	11.0	"	" " "	51–6.6	"	172	0/10	"	
		Other													
			B16	ip, 1 : 10	0743	"	21.1	"	1–9	4.0–0.25	4.0	143	4/10	"	
				" " "	0710	"	24.8	"	"	8.0–0.25	1.0	57	2/10	45	
			LL	sc," "	0715	"	18.6	"	"	4.0–0.13	0.25	49	0/10	"	
		Clinical form		iv, 1×10^5	0039	"	22.3	"	1, 5, 9	16.7–3.6	10.0	40	1/8	75	
		Saline and alcohol	Epend	ic, tumor frag	0018	"	20.4	"	1–5	16–1.0	1.0	6	0/10	60	
				" " "	0021	"	20.3	"	"	"	2.0	12	"	"	
95466	1-(2-Chloroethyl)-3-(2,6-dioxo-3-piperidyl)-1-nitrosourea	Other	L1210	ip, 1×10^5	2609	"	9.2	"	2 only	750–8.0	16	226	6/6	Death	
				" "	2625	"	8.6	"	" "	6–0.5	6.0	103	2/6	"	
				ic, 1×10^4	0115	"	8.5	"	" "	36–12	24	235	8/10	"	
				" "	0120	"	8.7	"	" "	44–5.5	33	197	10/10	"	
				iv, 1×10^5	0104	"	7.0	"	" "	35–2.1	17	328	4/10	45	
				iv, 1×10^7	0103	"	4.0	"	" "	"	35	470	2/10	"	
		Saline and Tween 80	P388	ip, 1×10^6	2486	"	11.0	"	1, 5, 9	9.0–4.0	9.0	172	4/6	30	
		Saline		" "	2586	"	"	"	" " "	4.0–0.5	4.0	163	2/6	"	
		Saline and Tween 80		ic, 1×10^7	0007	"	6.3	"	1 only	45–8.0	13.0	276	1/10	60	
				ic, 1×10^6	0008	"	7.4	"	" "	"	20	318	"	"	
			B16	ip, 1 : 10	0477	"	25.1	"	1–9	6.3–1.6	1.6	51	0/10	"	

APPENDIX I.—*Results of experimental studies in the United States with drugs developed here* [a] *(Continued)*

NSC No.	Compound	Drug vehicle	Tumor	Site and inoculum	Expt. No.	Parameter of effect [b]	Controls	Treatment		Doses, mg/kg/injection		Percent ILS or tumor inhibition	Survivors/total	Day of evaluation	ED50, μg/ml
								Route	Schedule, days	Tested	Optimal				
95466	1-(2-Chloroethyl)-3-(2,6-dioxo-3-piperidyl)-1-nitrosourea	Saline	B16	ip, 1 : 10	0518	MST	22.0	ip	1–9	2.4–0.7	1.6	65	0/10	60	
			Epend	ic, tumor frag	0116	"	15.2	"	1–5	40–2.5	2.5	295	6/6	"	
				" " "	0138	"	23.9	"	"	1.6–1.1	1.6	314	5/6	99	
		Gum arabic	LL	iv, 1 × 10^6	0009	"	21.9	"	2 only	23–7.6	15.0	161	8/9	59	
		Saline		sc, "	0105	"	23.0	"	1 only	80–5.0	40	56	2/10	60	
		Other		" "	0134	"	26.9	"	" "	"	20	41	1/10	"	
			KB		0692										88
45388	Dacarbazine	CMC	L1210	ip, 1 × 10^5	1225	"	9.4	"	1–9	400–50	200	94	0/10	Death	
		Other		" "	P371	"	9.7	"	"	400–25	"	70	0/6	30	
		Saline	L1210	ic, 1 × 10^5	0022	"	7.7	"	1–7	320–20	160	33	"	"	
		CMC		iv, 1 × 10^7	C259	"	8.9	"	2 only	900–176	900	111	0/10	45	
		Steroid susp	L1210	sc, 1 × 10^6	0035	"	8.3	"	1–9	300–75	150	28	"	30	
		Saline	P388	ip, 1 × 10^6	0052	"	12.0	"	1–10	200–25	100	54	0/6	Death	
		Klucel	B16	ip, 1 : 10	0012	"	16.0	"	1–9	300–37.5	300	43	"	60	
		Saline		" " "	0022	"	14.0	"	"	"	"	67	"	"	
		Saline	B16	sc, 1 : 10	0016	"	26.5	"	"	"	"	69	"	"	
		and Tween 80		" " "	0017	"	"	"	"	"	"	75	"	"	
		Klucel	LL	im, 1 × 10^6	0140	"	22.5	"	2–12	500–23	23	31	0/8	40	
		Saline		sc, 1 : 5	0015	"	36.5	"	8–16	300–37.5	25	"	4/10	60	
		Klucel	Epend	sc, tumor frag	0087	"	22.0	"	1–9	400–25	400	172	5/10	"	
			Colon-38	" " "	0018	Tumor wt	991 mg	"	7, 14, 21	"	"	76 [d]	—	20	

[a] ED50 = median inhibitory concentration; MST = mean survival time; ic = intracerebrally; LL = Lewis lung; q = every; frag = fragment; AK leuk (Spont) = AK leukemia (Spontaneous); Epend = ependymoblastoma; C3H mam = C3H mammary; susp = suspension; RCS = reticular cell sarcoma; CMC = carboxymethyl cellulose; DMSO = dimethyl sulfoxide; Clinical form = clinical formulation.

[b] MST value for controls is given in days.

[c] Other signifies other than standard vehicle was used. Reader is directed to Instruction 14 of the Drug Evaluation Branch, Division of Cancer Treatment, National Cancer Institute.

[d] Tumor was inhibited.

APPENDIX II.—*Results of experimental studies in the United States with drugs developed in the Soviet Union* [a]

NSC No.	Compound	Drug vehicle	Tumor	Site and inoculum	Expt. No.	Parameter of effect [b]	Controls	Treatment: Route	Treatment: Schedule, days	Doses, mg/kg/injection: Tested	Doses, mg/kg/injection: Optimal	Percent ILS or tumor inhibition	Survivors/total	Day of evaluation	ED50, μg/ml
44629	Dopan	CMC	L1210	ip, 1 × 10^5	0971	MST	8.9	ip	1–death	2.00–0.6	1.3	30	0/7	Death	
		Saline		" "	0975	"	8.6	"	" "	4.00–0.50	2.0	70	0/6	"	
				" "	0975	"	"	sc	" "	"	"	45	"	"	
				" "	0986	"	8.8	iv	1–6	32.0–4.0	16	"	"	"	
				" "	1002	"	9.1	Oral	1–death	128–32	32	29	"	"	
				sc, 1 × 10^6	0170	"	9.5	sc	8–death	39–5.0	14	42	0/10	"	
				" "	0185	"	11.0	"	" "	65–8.4	39	18	"	"	
			P388	ip, 1 × 10^6	0041	"	12.0	ip	1–10	4.0–5.0	1.0	75	0/6	"	
				" "	0046	"	11.0	"	"	"	4.0	118	"	"	
		Klucel		sc, 1 × 10^6	0006	"	17.9	"	1–9	"	0.5	41	0/10	30	
			B16	ip, 1 : 10	0198	"	21.2	"	"	"	"	55	1/10	60	
				sc, " "	0107	"	20.6	"	"	"	1.0	35	0/10	"	
			LL	" tumor frag	0121	"	23.5	"	"	"	"	26	"	"	
		Saline	Gardner	ip, 1 × 10^6	0035	"	13.5	"	1–10	"	4.0	100	0/6	Death	
				" "	0037	"	14.0	"	"	2.0–0.25	2.0	32	"	"	
				" "	0041	"	13.0	"	"	4.0–0.5	"	50	"	"	
		CMC	P388	" "	0038	"	9.1	"	1–death	0.5–0.06	0.5	28	"	"	
				" "	0042	"	8.5	"	" "	4.0–1.0	4.0	72	"	"	
			P335	ip, 1 × 10^6	0035	"	9.5	"	" "	8.0–1.0	2.0	61	"	"	
				" "	0038	"	9.9	"	" "	2.0–0.25	"	46	"	"	
		Saline	P1081	ip, 1 × 10^6	0027	"	9.0	"	1–10	4.0–0.5	"	233	3/6	"	
				" "	0033	"	10.0	"	"	"	0.5	40	0/6	"	
			KB		0258										3.6
73754	Fluoro-dopan	Klucel	L1210	ip, 1 × 10^5	2137	"	8.4	"	1, 5, 9	180–23	65	29	0/8	30	
		Saline		" "	7072	"	9.2	"	" " "	180–8.4	39	26	0/10	"	
		Acid–saline		" "	7566	"	8.0	Oral	1, 9 (q 3 hr)	128–8.0	32	31	"	60	
		Saline	P388	ip, 1 × 10^6	2220	"	12.0	ip	1–9	80–5.0	10	62	"	30	
		Klucel		" "	0986	"	11.0	"	"	"	"	72	0/6	"	
		Acid–saline		" "	2813	"	11.2	sc	"	32–2.0	32	37	0/10	60	
				" "	2829	"	11.0	Oral	1, 5, 9	256–16	128	27	"	"	
		Klucel	P388	sc, 1 × 10^6	0004	"	17.9	ip	1–9	28–3.5	7.0	24	"	45	
				ic, 1 × 10^5	0004	"	9.0	"	"	"	14	50	"	30	
			B16	ip, 1 : 10	0030	"	20	"	"	80–5.0	10	35	0/6	60	
		Saline and Tween 80		" " "	0382	"	"	"	"	39–1.8	14	65	0/10	45	
		Klucel		sc, " "	0105	"	23	"	"	28–3.5	"	28	0/7	60	
		Water		ic, 1 × 10^5	0018	"	12.4	"	"	64–2.0	8.0	12	0/6	30	

		Saline and Tween 80	LL	sc, tumor frag	0057	"	22.5	"	1, 5, 9	180–23	23	22	0/10	61	
		Saline	Epend	ic, " "	0118	"	18.3	"	1–5	48–3.0	12	439	3/6	99	
		Klucel		" " "	0212	"	22.3	"	"	64–2.0	16	169	9/10	60	
		Olive oil	S180	sc, " "	3591	Tumor wt	994 mg	sc	1–7	31	31	37	0/6	8	
				" " "	3577	" "	169 "	"	"	"	"	50	"	"	
			KB		0403										20
					0110										100
14210	Sarcolysin	Alkali and saline	L1210	ip, 1×10^5	0713	MST	9.3	ip	1–10	32–2.0	8.0	91	"	Death	
				" "	0722	"	8.9	"	"	"	4.0	55	"	"	
		Other	P388	ip, 1×10^6	0050	"	11.0	"	"	16–2.0	2.0	200	4/6	"	
		Klucel	P388	sc, "	0001	"	19.2	"	1–9	4.0–0.5	4.0	40	0/10	30	
		Saline	B16	ip, 1 : 10	0016	"	14.0	"	"	32–4.0	8.0	278	3/10	60	
				" " "	0043	"	16.0	"	"	16–4.0	16.0	168	0/10	"	
		Klucel		sc, " "	0105	"	23.0	"	"	4.0–0.5	4.0	73	0/8	"	
			LL	im, 1×10^6	0150	"	19.5	"	1–11	16–1.0	1.0	10	"	49	
		MC	Ca-755	sc, tumor frag	2475	Tumor wt	1,003 mg	"	"	16–1.0	8.0	94	0/10	12	
				" " "	2388	" "	1,016 "	"	"	50–6.3	6.3	95	"	"	
		Klucel	C3H mam	" " "	0004	MST	35.4	"	2 only	14–7.0	14.0	58	"	64	
			S180	" " "	0303	Tumor wt	1,409 mg	"	1–7 (q 12 hr)	5.0–0.3	5.0	78	0/6	8	
		Acid–saline		" " "	0475	" "	828 "	"	"	10–0.6	2.5	71	"	"	
			Ehrlich	ip, 1×10^6	0022	" "	3.7 g	"	1–11	10–0.1	10	98	0/10	12	
				" "	0075	" "	5.7 "	"	"	8.0–2.0	8.0	99	0/6	"	
		Saline	Epend	ic, tumor frag	0058	MST	19.0	"	1–5	2.5–0.62	2.5	23	"	30	
			Gardner	ip, 1×10^6	0015	"	10.0	"	1–10	16–2.0	8.0	40	"	Death	
				" "	0014	"	"	"	"	"	"	60	"	"	
			Hep 129	sc, tumor frag	0120	Tumor wt	1,389 mg	"	1–5	12–2.7	5.2	64	"	15	
			AK leuk	ip, spleen susp	0043	MST	8.0	"	1–10	16–2.0	8.0	50	"	Death	
		Other		" " "	0046	"	"	"	"	"	"	85	"	"	
		Saline	Mecca L	ip, 1×10^6	0014	"	12.5	"	"	"	4.0	124	"	"	
				" "	0015	"	10.0	"	"	"	2.0	90	"	"	
		Alkali	P-1534	ip, 1 : 10	0008	"	10.5	"	"	32–2.0	4.0	23	"	"	
		and saline	P-1534	ip, 1 : 10	0010	"	10.9	"	"	"	2.0	32	"	"	
		Other	P815	ip, 1×10^6	0039	"	10.0	"	"	16–2.0	"	25	"	"	
			KB		0007										> 100
					0369										< 1.0
167780	Asaley	Saline and Tween 80	L1210	ip, 1×10^5	9157	"	9.0	ip	1, 5, 9	256–2.0	64	58	"	30	
		Klucel		sc, 1×10^6	0052	"	9.1	sc	5–13	256–1.0	256	62	0/10	"	
				" "	0054	"	"	"	"	384–113	384	58	"	"	

APPENDIX II.—*Results of experimental studies in the United States with drugs developed in the Soviet Union* [a] *(Continued)*

NSC No.	Compound	Drug vehicle	Tumor	Site and inoculum	Expt. No.	Parameter of effect [b]	Controls	Treatment		Doses, mg/kg injection		Percent ILS or tumor inhibition	Survivors/ total	Day of evaluation	ED50, μg/ml
								Route	Schedule, days	Tested	Optimal				
167780	Asaley	Saline and Tween 80	L1210	ic, 1×10^5	0026	MST	7.6	ip	1–9	256–2.0	128	18	0/6	30	
		Olive oil	P388	ip, 1×10^6	3061	"	11.0	"	"	"	32	75	"	35	
		Other		" "	3325	"	12.2	"	"	256–1.0	128	95	0/10	30	
		Klucel		sc, "	0001	"	14.2	sc	5–13	"	64	"	"	40	
				" "	0003	"	18.0	"	"	"	"	50	"	60	
		Saline and Tween 80	P388	ic, 1×10^6	0016	"	9.7	ip	1–9	256–2.0	"	54	0/6	30	
		Saline	B16	ip, 1 : 10	0473	"	17.2	"	"	256–8.0	32	38	0/10	60	
		Other		sc, 1 : 5	0246	"	30.0	"	"	256–1.0	2.0	3	"	"	
		Saline and Tween 80		ic, 1×10^5	0022	"	7.2	"	"	256–2.0	64	51	"	40	
		Klucel	LL	sc, tumor frag	0070	"	25	"	"	128–4.0	4.0	24	0/9	60	
		Other		" " "	0013	"	30.8	"	"	256–1.0	2.0	13	0/10	"	
		Klucel	Epend	ic, " "	0035	"	16.3	"	1–5	128–4.0	16	42	"	"	
			KB		1397										1.2
183736	Phenestrol	Saline	L1210	ip, 1×10^5	7696	"	8.9	"	2, 6	400–100	100	1	0/3	20	
		and		" "	8222	"	8.5	sc	1 only	800–25	"	2	0/6	30	
		Tween		" "	8222	"	"	Oral	1–9	400–25	25	14	"	"	
		80	P388	ip, 1×10^6	1809	"	10.5	ip	"	"	400	7	"	"	
		Klucel	B16	ip, 1 : 10	0193	"	19.0	"	"	25–6.3	12.5	10	0/10	60	
		Saline and Tween 80		sc, " "	0006	"	25.4	"	"	405–80	120	6	"	80	
		Klucel	LL	sc, tumor frag	0120	"	24.8	"	"	25–6.3	25	4	"	60	
183735	Distron	Saline	L1210	ip, 1×10^5	7924	"	8.8	"	"	405–80	180	10	"	30	
		and		" "	8221	"	8.4	"	"	200–12.5	200	15	0/6	"	
		Tween		" "	8221	"	"	sc	1 only	800–25	50	9	"	"	
		80		" "	8221	"	"	Oral	1–9	400–25	"	10	"	"	
		Klucel	L1210	sc, 1×10^5	0005	"	10.7	ip	"	400–50	200	21	0/10	"	
			P388	ip, 1×10^6	1537	"	11.7	"	"	"	100	86	0/6	"	
		Saline and Tween 80		" "	1843	"	11.3	"	"	300–59	88	103	"	"	

		Klucel		sc, "	0004	"	17.9	"	"	200–25	25	39	0/10	45
				ic, 1×10^5	0032	"	9.3	"	"	"	100	61	"	30
		Saline and Tween 80	B16	ip, 1 : 10	0807	"	26	"	"	80–5.0	5.0	34	3/10	45
				" " "	0824	"	18.7	"	"	80–2.5	80	17	0/10	"
				sc, " "	0006	"	25.4	"	"	405–80	"	"	"	80
		Klucel	LL	sc, tumor frag	0118	"	26.6	"	"	400–50	50	21	"	60
183734	Palphicerin	Saline	L1210	ip, 1×10^5	8220	"	8.8	"	1 only	800–25	800	53	0/6	30
		Other		" "	2894	"	9.1	"	"	1,600–200	400	29	"	"
		Saline		" "	8220	"	8.8	sc	1–9	200–12.5	100	36	"	"
				" "	8220	"	"	Oral	"	400–25	50	38	"	"
		Saline		sc, 1×10^6	0005	"	10.7	ip	"	80–10	80	28	0/8	"
		and Tween 80	P388	ip, 1×10^6	1809	"	10.5	"	"	200–25	50	157	2/6	"
				" "	1843	"	11.3	"	"	100–6.3	25	132	1/6	"
		Saline and Tween 80	P388	sc, 1×10^6	0002	"	19.2	"	"	100–12.5	50	35	1/10	"
				ic, 1×10^5	0032	"	9.3	"	"	"	100	29	0/10	"
			B16	ip, 1 : 10	0563	"	20.3	"	"	80–15	35	57	"	60
				sc, " "	0006	"	25.4	"	"	"	23	6	"	80
			LL	sc, tumor frag	0120	"	24.8	"	"	25–3.1	12.5	4	"	60
166100	Prospidine	Water	L1210	ip, 1×10^5	3421	"	9.3	"	"	300–59	132	7	0/6	30
				" "	0225	"	9.2	"	"	300–38	150	14	"	60
		Saline		sc, "	0005	"	10.7	"	"	320–40	320	"	0/9	30
		Water	P388	ip, 1×10^6	1210	"	11.0	"	"	400–100	200	59	0/6	"
				" "	1844	"	11.3	"	"	300–88	"	53	"	"
		Saline		sc, 1×10^6	0003	"	17.9	"	"	320–40	160	21	0/10	"
				" "	0005	"	18.2	"	"	400–50	400	26	"	"
				ic, 1×10^5	0032	"	9.3	"	"	"	"	1	"	"
		Water	B16	ip, 1 : 10	0054	"	21.0	"	"	300–37.5	150	54	0/6	60
				" " "	0117	"	19.3	"	"	225–66	66	72	0/10	"
		Saline		sc, " "	0106	"	19.4	"	"	400–50	200	77	0/9	"
				" " "	0107	"	20.6	"	"	400–100	"	119	0/10	"
				" " "	0120	"	24.8	"	"	320–40	320	57	"	"
216135	Fotrin		L1210	ip, 1×10^5	2078	"	10.1	"	"	400–25	25	56	0/6	30
				" "	2828	"	9.7	"	"	200–6.3	"	64	0/10	60
			P388	ip, 1×10^6	4209	"	9.9	"	"	64–4.0	32	135	0/6	30
				" "	1846	"	11.5	"	"	100–3.1	25	160	0/10	60
				sc, "	0006	"	17.9	"	"	100–12.5	"	52	2/10	30
			B16	ip, 1 : 10	0127	"	19.8	"	"	100–3.1	"	117	0/10	60
				" " "	0136	"	20.9	"	"	"	"	88	"	"
				sc, " "	0004	"	18.7	"	"	20–1.3	20	39	"	"
			LL	sc, tumor frag	0003	"	27.3	"	1–17 (q 2 days)	200–6.3	12.5	16	"	"
167781	Diiodoben-zotepa		L1210	ip, 1×10^5	5152	"	8.6	"	1–9	512–2.0	16	76	0/6	30
				" "	2819	"	9.0	"	"	"	64	83	0/10	"
				" "	5150	"	9.7	"	1 only	"	512	49	0/6	"

APPENDIX II.—*Results of experimental studies in the United States with drugs developed in the Soviet Union* [a] *(Continued)*

NSC No.	Compound	Drug vehicle	Tumor	Site and inoculum	Expt. No.	Parameter of effect [b]	Controls	Treatment		Doses, mg/kg/injection		Percent ILS or tumor inhibition	Survivors/total	Day of evaluation	ED50, μg/ml
								Route	Schedule, days	Tested	Optimal				
167781	Diiodobenzotepa	Saline and Tween 80	L1210	ip, 1×10^5	5727	MST	9.2	Oral	1 only	512–2.0	512	33	0/10	30	
		Klucel		sc, "	0005	"	10.7	ip	1–9	64–8.0	32	61	"	"	
		Saline	P388	ip, 1×10^6	4991	"	9.9	"	"	512–2.0	8.0	132	0/6	"	
				" "	1796	"	10.9	"	"	"	64	170	0/10	60	
				" "	1806	"	11.8	Oral	1 only	"	256	61	"	"	
		Klucel	P388	sc, "	0002	"	19.2	ip	1–9	64–8.0	32	54	5/10	30	
		Saline	B16	ip, 1 : 10	0063	"	25.1	"	1–17 (q 2 days)	512–2.0	16	50	0/10	60	
		Saline		" " "	0297	"	21.6	"	" " "	"	32	48	"	"	
		and Tween 80		sc, 1 : 5	0296	"	27.2	"	" " "	"	"	35	"	"	
		Saline		sc, 1 : 10	0003	"	22.3	"	" " "	"	64	47	"	"	
		Saline and Tween 80	LL	sc, tumor frag	0059	"	25.4	"	" " "	"	8.0	17	"	"	
148958	Ftorafur	Klucel	L1210	ip, 1×10^5	2137	"	8.4	"	1, 5, 9	833–108	833	88	0/8	30	
		Other		" "	2502	"	8.7	"	" " "	833–39	500	70	"	"	
		Water		sc, 1×10^6	0789	"	9.1	"	" " "	833–108	833	68	"	21	
		Other		ip, 1×10^5	2502	"	8.7	sc	" " "	833–39	500	98	1/8	30	
				" "	"	"	"	Oral	" " "	"	833	64	0/8	"	
		Water		ic, 1×10^6	0007	"	10.1	ip	" " "	833–65	500	38	"	"	
		Klucel	P388	ip, "	1614	"	10.8	"	1 only	1,436–316	1,436	37	0/10	45	
				" "	1745	"	11.9	"	" "	"	957	34	"	"	
		Other		iv, "	0016	"	10.9	"	1, 5, 9	500–200	500	58	"	60	
		Water	B16	ip, tumor susp	0002	"	10.2	sc	" " "	833–108	300	48	"	"	
		Saline		sc, 1 : 5	0003	"	28.8	ip	" " "	"	108	18	"	"	
			LL	im, 1×10^6	0258	"	26.0	"	1–11	300–39	65	19	0/8	47	
216134	Tomizin		L1210	ip, 1×10^5	2078	"	10.1	"	1–9	400–25	50	1	0/6	30	
				sc, "	0008	"	11.6	"	"	100–12.5	12.5	2	0/10	"	
			P388	ip, 1×10^6	1756	"	11.2	"	"	"	50	5	0/6	"	
				sc, "	0006	"	17.9	"	"	"	12.5	2	0/10	"	
			B16	ip, 1 : 10	0110	"	20.0	"	"	"	25.0	100	"	60	
			LL	sc, tumor frag	0120	"	23.5	"	"	"	"	22	"	"	
180024	Carminomycin		L1210	ip, 1×10^5	7595	"	7.8	"	1 only	3.00–0.39	0.65	53	"	30	
				" "	0006	"	8.7	"	1, 5, 9	1.0–0.13	1.0	12	"	"	

			P388	ip, 1×10^6	4594	"	11.4	"	1 only	1.2–0.16	0.72	80	"	60
				" "	2844	"	11.0	"	" "	3.0–0.39	0.65	72	"	"
				ic, 1×10^5	0032	"	9.3	"	1, 5, 9	1.0–0.13	1.0	10	"	30
		Clinical form	B16	ip, 1 : 10	0131	"	24.8	"	1–9	1.0–0.03	0.25	38	1/10	60
				sc, tumor susp	0091	"	19.3	"	"	"	0.13	11	0/9	"
		Saline	LL	sc, tumor frag	0067	"	31	"	"	"	0.03	3	0/10	"
76411	Olivomycin	Other	L1210	ip, 1×10^5	4085	"	9.2	"	"	2.0–0.25	2.0	66	0/6	30
		Saline and Tween 80		sc, "	0008	"	11.6	"	"	4.0–0.5	"	31	0/10	"
		Saline	P388	ip, 1×10^6	0090	"	11.0	"	1–10	12–0.38	1.5	118	0/6	Death
				" "	0319	"	"	"	"	4–0.25	1.0	127	"	30
		Saline		sc, "	0006	"	17.9	"	1–9	4–0.50	2.0	30	0/10	"
		and	B16	ip, 1 : 10	0198	"	21.2	"	"	4–0.5	"	79	1/10	60
		Tween		sc, " "	0107	"	20.6	"	"	"	"	40	0/10	"
		80	LL	sc, tumor frag	0121	"	23.5	"	"	"	0.5	−3	"	"
196869	Aton		L1210	ip, 1×10^5	7053	"	9.3	"	"	400–50	200	2	0/6	30
			P388	" 1×10^6	1955	"	12.3	"	"	"	"	13	"	"
			B16	" 1 : 10	0217	"	20.7	"	"	"	100	−2	0/10	60
183737	Chanerol	Salinc	L1210	ip, 1×10^5	P124	"	8.3	"	1–5	11.3–2.2	2.2	8	0/6	"
				" "	8223	"	8.6	sc	1–9	16–0.5	1.0	5	0/10	"
				" "	"	"	"	Oral	"	32–1.0	32	4	"	"
			P388	ip, 1×10^6	2937	"	11.0	ip	"	8–0.5	2.0	0	0/3	30
			B16	ip, 1 : 10	0563	"	20.3	"	"	7.5–1.5	3.3	2	0/10	60
				sc, " "	0006	"	25.4	"	"	"	1.5	18	"	80
			LL	sc, tumor frag	0004	"	29.7	"	1–17 (q 2 days)	16–0.5	8	5	"	60
183738	Colchizin		L1210	ip, 1×10^5	8224	"	9.0	"	1–9	200–12.5	200	18	0/6	30
				" "	P124	"	8.3	"	1–5	270–53	180	"	"	"
				" "	8224	"	9.0	sc	1–9	200–12.5	200	−6	"	"
			P388	ip, 1×10^6	3268	"	10.8	ip	"	270–53	270	50	"	"
				" "	1844	"	11.3	"	"	300–59	200	70	"	"
			B16	ip, 1 : 10	0563	"	20.3	"	"	180–35	53	6	0/10	60
				sc, " "	0006	"	25.4	"	"	"	35	29	1/10	80
		Klucel	LL	sc, tumor frag	0118	"	26.6	"	"	400–50	100	2	0/10	60
271276	Diazan	Other	L1210	ip, 1×10^5	7096	"	8.6	"	"	50–6.3	6.3	41	0/6	30
		Salinc	L1210	ip, "	7108	"	"	"	"	6.00–0.75	3.0	48	"	"
			P388	ip, 1×10^6	2263	"	10.0	"	"	"	"	70	"	"
			B16	ip, 1 : 10	0205	"	17.6	"	"	"	0.75	43	0/10	60
269146	Variamycin		L1210	ip, 1×10^5	7053	"	9.3	"	"	3.0–0.38	0.75	15	0/6	30
			P388	ip, 1×10^6	1955	"	12.3	"	"	"	1.5	70	"	"
		Water	B16	ip, 1 : 10	0214	"	23.1	"	"	"	"	34	0/10	60
			LL	sc, tumor frag	0128	"	23.4	"	"	"	3.0	28	"	"

APPENDIX II.—*Results of experimental studies in the United States with drugs developed in the Soviet Union* [a] *(Continued)*

NSC No.	Compound	Drug vehicle	Tumor	Site and inoculum	Expt. No.	Parameter of effect [b]	Controls	Treatment: Route	Treatment: Schedule, days	Doses, mg/kg/injection: Tested	Doses, mg/kg/injection: Optimal	Percent ILS or tumor inhibition	Survivors/total	Day of evaluation	ED50, μg/ml
99733	Reumycin	Water	L1210	ip, 1×10^5	7053	MST	9.3	ip	1–9	3.0–0.38	0.75	4	0/6	60	
			P388	ip, 1×10^6	1955	"	12.3	"	"	"	3.0	0	"	"	
			B16	ip, 1 : 10	0214	"	23.1	"	"	"	0.75	18	0/10	"	
275653	Agavoside	Saline	L1210	ip, 1×10^5	7099	"	8.3	"	"	10–1.3	1.3	−3	"	"	
			P388	ip, 1×10^6	2251	"	11.6	"	"	40–5	5.0	0	0/8	"	
			B16	ip, 1 : 10	0217	"	20.7	"	"	5.0–0.62	"	10	0/10	"	
			LL	sc, tumor frag	0126	"	19.6	"	"	"	0.62	−2	"	"	
23471	Digitonin		L1210	ip, 1×10^5	7099	"	8.3	"	"	40–5.0	40	2	"	30	
			P388	ip, 1×10^6	2251	"	11.6	"	"	5.0–0.62	0.62	1	"	"	
			B16	ip, 1 : 10	0214	"	23.1	"	"	"	"	9	"	60	
			LL	sc, tumor frag	0128	"	23.4	"	"	"	"	29	"	"	
275654	Funkioside		L1210	ip, 1×10^5	7099	"	8.3	"	"	40–5.0	20	8	"	30	
			P388	ip, 1×10^6	2251	"	11.6	"	"	5–0.6	2.5	−5	"	"	
			B16	ip, 1 : 10	0214	"	23.1	"	"	"	"	3	1/10	60	
			LL	sc, tumor frag	0128	"	23.4	"	"	"	5.0	36	0/10	"	
275655	Vitalboside		L1210	ip, 1×10^5	7099	"	8.3	"	"	40–5.0	10	1	"	"	
			P388	ip, 1×10^6	2235	"	11.9	"	"	"	"	−1	"	"	
			B16	ip, 1 : 10	0218	"	19.6	"	"	"	"	−12	"	"	
			LL	sc, tumor frag	0127	"	22.4	"	"	"	5	20	"	"	
275652	Gluco-mannan		L1210	ip, 1×10^5	7099	"	8.3	"	"	100–12.5	100	−4	"	"	
			P388	ip, 1×10^6	2235	"	11.9	"	"	"	"	8	"	"	
				" "	2251	"	11.6	"	"	200	200	0	0/8	"	
			B16	ip, 1 : 10	0217	"	20.7	"	"	100–12.5	25	2	0/10	"	
			LL	sc, tumor frag	0126	"	19.6	"	"	"	"	"	"	"	
275656	Dioxadet		L1210	ip, 1×10^5	7108	"	8.6	"	"	7.5–2.5	2.5	68	0/6	30	
				" "	7102	"	8.2	"	"	5.0–0.6	"	121	0/10	"	
			P388	ip, 1×10^6	2251	"	11.6	"	"	"	"	129	1/10	"	
				" "	2375	"	11.2	"	"	3.8–0.6	"	99	0/6	"	
			B16	ip, 1 : 10	0214	"	23.1	"	"	5.0–0.6	"	94	3/10	60	
				" " "	0218	"	19.6	"	"	"	1.25	62	0/10	"	
			LL	sc, tumor frag	0128	"	23.4	"	"	"	0.62	19	"	"	
275658	Phenthy-rine		L1210	ip, 1×10^5	7099	"	8.3	"	"	40–5.0	20	31	"	30	
				" "	7108	"	8.6	"	"	20–10.0	"	16	0/6	"	
			P388	ip, 1×10^6	2235	"	11.9	"	"	40–5.0	10	70	0/10	"	
				" "	2251	"	11.6	"	"	20–2.5	"	72	"	"	

		B16	ip, 1 : 10	0214	"	23.1	"	"	"	"		3/10	60
		LL	sc, tumor frag	0128	"	23.4	"	"	"	"	19	0/10	"
23909	Methylnitrosourea	L1210	ip, 1×10^5	0829	"	11.3	"	1–death	14–11	11	88	0/6	Death
			" "	0912	"	9.7	"	"	20–5.0	10	87	"	"
		L1210	sc, 1×10^6	253	"	9.0	"	6–death	180–14	39	61	0/10	"
	Saline and Tween 80	P388	ip, 1×10^6	2481	"	11.0	"	1–9	50–12.5	12.5	59	0/6	30
			" "	2847	"	12.0	"	"	37.5–16.5	37.5	54	1/6	"
	Saline	B16	ip, 1 : 10	0594	"	19.2	"	"	25–3.1	12.5	45	0/10	45
			" " "	0088	"	20.4	"	"	50–3.1	"	43	"	60
		LL	sc, tumor frag	0017	"	25.5	"	1 only	160–5.0	40	24	"	"
		Epend	ic, tumor frag	0181	"	20.0	"	1–5	8.0–0.25	8.0	349	4/6	90

[a] ED50 = median inhibitory concentration; CMC = carboxymethyl cellulose; MST = mean survival time; LL = Lewis lung; frag = fragment; leuk = leukemia; ic = intracerebrally; mam = mammary; Epend = ependymoblastoma; susp = suspension; Mecca L = Mecca lymphoma; Clinical form = clinical formulation.

[b] MST value for controls is given in days.

APPENDIX III.—*Results of experimental studies in the Soviet Union with drugs developed there* [a]

NSC No.	Compound	Drug vehicle	Tumor	Site and inoculum	Expt. No.	Parameter of effect	Controls	Treatment: Route	Treatment: Schedule, days	Doses, mg/kg/injection: Tested	Doses, mg/kg/injection: Optimal	ILS or Percent tumor inhibition	Survivors/total	Day of evaluation	ED50, μg/ml
44629	Dopan	Boiled starch	L1210	ip, 1 × 10^6 cells	1	MST	8.5 days	Oral	2–6	0.4		7	0/6	19	
					2	"	8.0 "	ip	1–5	0.5		35	0/5	12	
					3	"	7.3 "	"	1–8	0.4		63	0/10	13	
			La	" " "	4	"	7.2 "	"	1–7	"		68	0/8	15	
			MOPC 406	" 50 mg tumor susp	5, 6, 7	"	14.7 "	Oral	2–6	"		7	0/7	37	
						"	19.8 "	ip	3–14	"		88	0/8	46	
			LL	sc, " " " "	8	Tumor vol	970 mm^3	"	2,6	"		13	6/6	7	
						" "	9,926 "	"	" "	"		+6	"	14	
						" "	24,116 "	"	" "	"		12	5/6	22	
						MST	24.5 days	"	" "	"		0	1/6	32	
			Ca-755	" " " " "	9	Tumor vol	1,137 mm^3	Oral	2–6	"		7	6/6	7	
						" "	6,631 "	"	"	"		27	"	13	
						" "	14,800 "	"	"	"		+84	4/6	21	
						MST	22.0 days	"	"	"		18	0/6	41	
			AKA-TOL	" " " " "	10, 11	Tumor vol	323 mm^3	"	"	"		+242	7/7	7	
						" "	1,506 "	"	"	"		+60	"	13	
						" "	8,577 "	"	"	"		+6	"	29	
						MST	54 days	"	"	"		0	0/7	79	
			RShM-5	" " " " "	12, 13	Tumor vol	184 mm^3	"	"	0.2–0.4		+14	6/6	7	
						" "	1,308 "	"	"	"		+18	"	13	
						" "	3,644 "	"	"	"		28	"	17	
						" "	13,123 "	"	"	"		3	5/6	31	
			S37	" 10^6 cells	14	MST	41.4 days	"	"	"		0	0/6	57	
						Tumor vol	558 mm^3	"	2,6	0.6		45	8/9	10	
						" "	2,414 "	"	" "	"		21	"	20	
						" "	558 "	"	2–6	0.4		90	9/9	10	
						" "	1,490 "	"	"	"		80	"	14	
						" "	2,414 "	"	"	"		71	"	20	
			S37			NA content									< 1
			L5178Y			" "									20–10
			Ehrlich			" "									< 1
			NK/Ly			" "									5–1
73754	Fluoro-dopan	Boiled starch	L1210	ip, 10^6 cells	15	MST	8.5 days	"	2,6	25–400	100	18	0/3	69	
			La	" " "	16	"	18.8 "	"	1,5	60		16	0/8	56	
			MOPC 406	ip, 50 mg tumor susp	17		14.7 "	"	2,6	"		0	0/6	37	
			LL	sc, " " " "	18	Tumor vol	1,518 mm^3	"	" "	"		76	6/6	7	
						" "	11,514 "	"	" "	"		75	5/6	13	
						MST	19.7 days	"	" "	"		10	0/6	35	
			CA-755	" " " " "	784	Tumor vol	568 mm^3	"	" "	"		50	8/8	7	
						" "	8,769 "	"	" "	"		46	"	13	
						" "	25,060 "	"	" "	"		57	7/8	18	
						MST	24.7 days	"	" "	"		7	0/8	48	

			Ca-755	" " " " "	19, 20	Tumor vol	193 mm³	"	" "	"		86	10/10	7		
						" "	2,636 "	"	" "	"		88	"	13		
						" "	22,235 "	"	" "	"		90	"	23		
						" "	30,025 "	"	" "	"		76	9/10	30		
						MST	29.1 days	"	" "	"		34	1/10	62		
			AKA-TOL	" " " " "	21	Tumor vol	292 mm³	"	" "	"		89	8/8	7		
						" "	4,196 "	"	" "	"		99.2	"	13		
						" "	18,062 "	"	" "	"		95	"	20		
		Boiled starch	AKA-TOL	" " " " "	813	Tumor vol	34,133 "	"	" "	"		90	5/8	27		
						MST	31.2 days	"	" "	"		7	0/8	42		
			RShM-5	" " " " "	22	Tumor vol	1,308 mm³	"	" "	"		0	6/6	13		
							3,644 "	"	" "	"		44	"	17		
						MST	41.4 days	"	" "	"		20	0/6	57		
			CaOv			[³H]dThd incl									8	
			CaOv			NA content									15	
			CaOv			Pro "									25	
8806	Sar-colysin	Saline	L1210	ip, 10^6 cells	23, 24	MST	8.5 "	ip	" "	2.5–4.0	10	88	1/3	69		
				" " "	25	"	9.9 "	"	" "	7	7	107	3/6	21		
				" " "	25	"	9.9 "	"	2–6	2		56	0/6	"		
				" " "	26	"	7.6 "	"	2,6	7		51	2/6	13		
			La	" " "	27	"	7.1 "	"	1,5	"	"	227	0/4	46		
			MOPC 406	ip, 50 mg tumor susp	28, 29		15.1 "	"	2,6	"	"	132	5/6	38		
					30		17 "	"	" "	"		115	2/8	93		
			LL	sc, " " " "	31	Tumor vol	1,700 mm³	"	" "	"	"	81	6/6	7		
						" "	10,553 "	"	" "	"		87	"	14		
						" "	17,188 "	"	" "	"		44	"	22		
						MST	20.1 days	"	" "	"		79	1/6	41		
						Tumor vol	1,700 mm³	"	2–6	2		48	6/6	7		
						" "	10,553 "	"	"	"		60	"	14		
						" "	17,188 "	"	"	"		30	"	22		
					32	MST	20 days	"	"	"		45	0/6	41		
						Tumor vol	2,693 mm³	"	2,6	7	"	59	6/6	7		
						" "	14,775 "	"	" "	"	"	65	"	13		
						" "	18,001 "	"	" "	"	"	30	5/6	20		
						MST	21.3 days	"	" "	"	"	"	1/6	35		
						Tumor vol	2,693 mm³	"	2–6	2		20	6/6	7		
						" "	14,775 "	"	"	"		60	"	13		
						" "	18,001 "	"	"	"		12	4/6	20		
						MST	21.3 days	"	"	"		6	0/6	35		
			Ca-755	sc, " " " "	33	Tumor vol	992 mm³	"	2,6	7	7	96	5/5	7		
						" "	8,588 "	"	" "	"	"	98	"	11		
						" "	15,436 "	"	" "	"	"	91	"	14		
						MST	22.3 days	"	" "	"	"	29	1/5	33		
					34	Tumor vol	38 mm³	"	2,6,16,20	"	"	95	7/7	7		
						" "	3,562 "	"	" " " "	"	"	99.3	"	13		
						" "	10,407 "	"	" " " "	"	"	98	"	17		
						" "	19,849 "	"	" " " "	"	"	95	"	22		
						MST	25.5 days	"	" " " "	"	"	56	0/7	57		
					35	Tumor vol	210 mm³	"	2–6	0.5–4	4	91	6/6	7		

APPENDIX III.—*Results of experimental studies in the Soviet Union with drugs developed there* [a] *(Continued)*

NSC No.	Compound	Drug vehicle	Tumor	Site and inoculum	Expt. No.	Parameter of effect	Controls	Treatment: Route	Treatment: Schedule, days	Doses, mg/kg/injection: Tested	Doses, mg/kg/injection: Optimal	Percent ILS or tumor inhibition	Survivors/total	Day of evaluation	ED50, µg/ml
8806	Sarcolysin	Saline	Ca-755	sc, 50 mg tumor susp	35	Tumor vol	5,339 mm³	ip	2–6	0.5–4	4	68	6/6	14	
						" "	11,649 "	"	"	"	"	46	"	18	
						MST	24.4 days	"	"	"	"	37	0/6	45	
					36	Tumor vol	265 mm³	"	4–13	1.5		33	10/10	6	
						" "	6,718 "	"	"	"		64	"	14	
						" "	16,324 "	"	"	"		76	"	21	
						MST	28 days	"	"	"		59	0/10	85	
						Tumor vol	265 mm³	"	4,7,10,13	5		8	10/10	6	
						" "	6,718 "	"	" " " "	"		63	"	14	
						" "	16,324 "	"	" " " "	"		64	"	21	
						MST	28 days	"	" " " "	"		21	0/10	85	
						Tumor vol	265 mm³	"	4,14,24	10		60	10/10	6	
						" "	6,718 "	"	" " "	"		88	8/10	14	
						" "	16,324 "	"	" " "	"		90	"	20	
						MST	28 days	"	" " "	"		20	2/10	85	
			AKA-TOL	sc, " " " "	37, 38	Tumor vol	319 mm³	"	2,6	7	7	+10	7/7	7	
						" "	563 "	"	" "	"	"	56	"	13	
						" "	4,056 "	"	" "	"	"	65	"	24	
						" "	10,763 "	"	" "	"	"	35	"	39	
						MST	82.6 days	"	" "	"	"	22	0/7	108	
			RShM-5	sc, " " " "	39, 40	Tumor vol	270 mm³	"	" "	"	"	94	7/7	7	
						" "	1,429 "	"	" "	"	"	82	"	13	
						" "	3,863 "	"	" "	"	"	66	"	20	
						MST	39.6 days	"	" "	"	"	40	2/7	68	
			PRZh	im, " " " "	41	Tumor vol	6,148 mm³	"	" "	"	"	60	6/6	7	
						" "	11,231 "	"	" "	"	"	+20	4/6	13	
			S37	sc, 10^6 cells	42	" "	512 mm³	"	" "	"	"	84	8/8	7	
						" "	3,221 "	"	" "	"	"	98	"	13	
						" "	7,312 "	"	" "	"	"	91	"	20	
						" "	15,462 "	"	" "	"	"	82	"	27	
						MST	46.9 days	"	" "	"	"	57	4/8	105	
					43, 47	Tumor vol	180 mm³	"	" "	"		69	9/9	7	
					48	" "	1,241 "	"	" "	"		99.5	"	14	
						" "	6,415 "	"	" "	"		90	"	22	
						MST	64.6 days	"	" "	"		72	4/9	123	
						Tumor vol	180 mm³	"	2–6	2		83	9/9	7	
						" "	1,241 "	"	"	"		98	"	14	
						" "	6,515 "	"	"	"		91	"	22	
						MST	64.6 days	"	"	"		93	4/9	123	
			S-180	" 50 mg tumor susp	49, 50	Tumor vol	1,094 mm³	"	2,6	7		76	6/6	7	
						" "	5,123 "	"	" "	"		64	"	14	
						" "	9,017 "	"	" "	"		22	"	21	
						MST	34 days	"	" "	"		27	0/6	56	
			S37			NA content									10–1

			L5178Y				” ”								10–1
			Ehrlich				” ”								< 1
							” ”								< 1
			NK/Ly				” ”								
			CaOv	[^{3}H]dThd incl											< 1
			CaOv	NA content											5
			CaOv	Pro ”											20
167780	Asaley	Boiled starch	L1210	ip, 10^6 cells	61, 62	MST	8.5 days	Oral	” ”	120	35	0/6	19		
			La	” 3.5×10^6	63	”	11.2 ”	”	1,5	”	77	”	61		
			MOPC 406	” 50 mg tumor susp	64	”	14.7 ”	”	2,6	”	31	”	37		
			LL	sc, ” ” ” ”	65	Tumor vol	1,564 mm^3	”	2–6	40	76	6/6	7		
						” ”	11,764 ”	”	”	”	68	”	13		
						” ”	21,268 ”	”	”	”	43	”	31		
						MST	24.1 days	”	”	”	22	0/6	35		
					66	Tumor vol	2,397 mm^3	”	2,6	120	64	6/6	7		
						” ”	6,202 ”	”	” ”	”	54	5/6	13		
						” ”	12,582 ”	”	” ”	”	52	”	18		
						MST	33 days	”	” ”	”	14	0/7	50		
					67	Tumor vol	1,554 mm^3	”	” ”	”	68	6/6	7		
						” ”	11,764 ”	”	” ”	”	50	”	13		
						” ”	21,268 ”	”	” ”	”	47	5/6	21		
						MST	34.1 days	”	” ”	”	25	1/6	35		
			Ca-755	” ” ” ” ”	68, 69, 70	Tumor vol	135 mm^3	”	” ”	”	91	10/10	7		
						” ”	2,788 ”	”	” ”	”	68	”	13		
						” ”	10,618 ”	”	” ”	”	76	”	19		
						MST	33.2 days	”	” ”	”	12	1/10	81		
			AKA-TOL	” ” ” ” ”	71	Tumor vol	1,920 mm^3	”	” ”	”	64	6/6	12		
						” ”	4,091 ”	”	” ”	”	54	”	21		
						” ”	12,342 ”	”	” ”	”	36	”	35		
						MST	53 days	”	” ”	”	2	0/6	93		
			RShM-5	” ” ” ” ”	72	Tumor vol	111 mm^3	”	” ”	”	67	8/8	7		
						” ”	1,124 ”	”	” ”	”	88	”	14		
						” ”	6,689 ”	”	” ”	”	63	”	23		
						” ”	17,531 ”	”	” ”	”	59	7/8	32		
						MST	39.1 days	”	” ”	”	25	1/8	62		
						Tumor vol	111 mm^3	”	2–6	40	69	8/8	7		
						” ”	1,124 ”	”	”	”	81	”	14		
					814	” ”	6,689 ”	”	”	”	64	”	23		
						” ”	17,531 ”	”	”	”	59	6/8	32		
						MST	39.1 days	”	”	”	14	1/8	62		
			S37	sc, 10^6 cells	73	Tumor vol	512 mm^3	”	2,6	120	58	8/8	7		
						” ”	3,221 ”	”	” ”	”	94	”	13		
						” ”	7,312 ”	”	” ”	”	87	”	20		
						” ”	26,884 ”	”	” ”	”	81	”	34		
						MST	45.9 days	”	” ”	”	25	2/8	105		
			CaOv			[^{3}H]dThd incl									1
			CaOv			NA content									10
			CaOv			Pro ”									30

APPENDIX III.—*Results of experimental studies in the Soviet Union with drugs developed there* [a] *(Continued)*

NSC No.	Compound	Drug vehicle	Tumor	Site and inoculum	Expt. No.	Parameter of effect	Controls	Treatment Route	Treatment Schedule, days	Doses, mg/kg/injection Tested	Doses, mg/kg/injection Optimal	Percent ILS or tumor inhibition	Survivors/total	Day of evaluation	ED50, ug/ml
183736	Phenestrol	Olive oil	L1210	ip, 10^6 cells	74	MST	7.6 days	sc	2–6	100		14	0/6	13	
			La	ip, 5×10^6 cells	75	"	8.8 "	"	1–5	"		0	0/7	63	
			Ca-755	sc, 50 mg tumor susp	76, 77	Tumor vol	2,992 mm^3	"	3,6,9	300		42	10/10	7	
						Tumor wt	6.3 g	"	" " "	"		61	1/10	14	
						Tumor vol	641 mm^3	"	3,6,9,12	"		27	10/10	7	
						" "	4,314 "	"	" " " "	"		39	"	13	
						" "	7,824 "	"	" " " "	"		52	"	18	
			Ca-755	" " " " "	"	Tumor wt	8.0 g	"	" " " "	"		55	9/10	24	
			RShM-5	" " " " "	78	Tumor vol	1,013 mm^3	"	8,11,14,17, 20,23,26	"		43	9/9	12	
						" "	3,656 "	"	" " "	"		23	"	19	
						" "	7,742 "	"	" " "	"		26	"	27	
						MST	39.7 days	"	" " "	"		18	0/9	54	
			RShM-5	" " " " "	79	Tumor vol	425 mm^3	"	7,11,15,19	"		31	10/10	10	
						" "	1,366 "	"	" " " "	"		19	"	"	
						" "	4,051 "	"	" " " "	"		19	"	20	
						" "	9,824 "	"	" " " "	"		35	"	27	
						MST	41.4 days	"	" " " "	"		0	0/10	77	
			S180	" " " " "	80	Tumor vol	954 mm^3	"	2–6	100		+42	6/6	14	
						" "	3,536 "	"	"	"		+22	"	"	
						" "	11,676 "	"	"	"		+8	"	21	
						" "	29,478 "	"	"	"		29	5/6	30	
			CaOv			[^{3}H]dThd incl									100
			CaOv			NA content									> 100
			CaOv			Pro "									> 1,000
183735	Distron	Olive oil	L1210	sc, 10^6 cells	82	MST	8.5 days	"	2,6	25–400	400	41	0/3	69	
			MOPC 406	ip, 50 mg tumor susp	83	"	15.1 "	"	2–6	25		13	0/7	38	
			LL	sc, " " " "	84	Tumor vol	1,588 mm^3	"	"	50		40	6/6	7	
						" "	11,514 "	"	"	"		52	5/6	13	
						MST	19.7 days	"	"	"		0	0/6	59	
				" " " " "	85	Tumor vol	949 mm^3	"	4,14	150		3	10/10	7	
						" "	6,772 "	"	" "	"		45	8/10	15	
						" "	13,340 "	"	" "	"		48	"	24	
						MST	27.5 days	"	" "	"		9	0/10	40	
				" " " " "	86	Tumor vol	2,524 mm^3	"	2–6	25		4	6/6	7	
						" "	12,837 "	"	"	"		21	"	13	
						" "	26,178 "	"	"	"		16	"	22	
						MST	24 days	"	"	"		27	0/6	40	
			Ca-755	" " " " "	87, 88	Tumor vol	372 mm^3	"	"	25–50	25	77	9/9	7	
				" " " " "	89, 90	" "	8,970 "	"	"	"	"	99	"	13	
						" "	18,300 "	"	"	"	"	77	"	18	
						MST	23.3 days	"	"	"	"	46	0/9	93	

							Tumor vol	1,125 mm³	"	5,12,19,26	70	"	+11	9/9	9
							" "	4,680 "	"	" " " "	"		46	"	12
							" "	12,652 "	"	" " " "	"		68	"	17
							" "	17,506 "	"	" " " "	"		58	8/9	22
							" "	26,246 "	"	" " " "	"		35	"	29
			AKA-TOL	" " " " "		91	" "	5,872 "	"	2–6	25		54	7/7	7
							" "	8,334 "	"	"	"		46	"	13
							" "	17,140 "	"	"	"		56	"	20
							" "	21,826 "	"	"	"		+32	6/7	27
			RShM-5	" " " " "		92	" "	211 "	"	4,6,8,10, 12,14,16	50		29	11/11	5
							" "	943 "	"	" " "	"		45	"	12
							" "	2,616 "	"	" " "	"		52	"	18
							" "	4,452 "	"	" " "	"		59	"	24
							" "	6,696 "	"	" " "	"		58	"	32
			RShM-5			93	" "	2,572 mm³	"	10,17,24 31	100		60	10/10	14
							" "	5,326 "	"	" " " "	"		73	"	21
							" "	14,677 "	"	" " " "	"		80	"	27
							" "	22,854 "	"	" " " "	"		79	8/10	35
							MST	39 days	"	" " " "	"		8	0/10	73
						94	Tumor vol	425 mm³	"	7,17	150		29	10/10	10
							" "	4,051 "	"	" "	"		79	"	20
							" "	9,824 "	"	" "	"		75	7/10	27
							MST	41.4 days	"	" "	"		6	0/10	77
						95	Tumor vol	273 mm³	"	2–6	25		82	7/7	7
							" "	1,188 "	"	"	"		60	"	14
							" "	4,371 "	"	"	"		35	"	21
							MST	48.3 days	"	"	"		0	0/7	83
			S37	" 10^6 cells		96	Tumor vol	520 mm³	"	"	"		+20	6/7	7
							" "	2,827 "	"	"	"		46	"	13
							" "	8,618 "	"	"	"		44	"	28
							MST	56 days	"	"	"		4	4/7	80
			S180	" 50 mg tumor susp		97	Tumor vol	954 mm³	"	"	"		+74	6/6	7
							" "	3,536 "	"	"	"		+77	"	14
							" "	29,478 "	"	"	"		+16	5/6	30
183734	Palphi-cerin	Olive oil	L1210	ip, 10^6 cells		98	MST	7.6 days	"	"	"		18	0/6	13
			La	" 5×10^6 cells		99	"	8.8 "	"	1–5	"		22	0/7	63
			MOPC 406	" 50 mg tumor susp		100	"	15.1 "	"	2–6	"		41	"	38
			LL	sc, " " " "		101	Tumor vol	1,518 mm³	"	"	"		43	6/6	7
							" "	11,514 "	"	"	"		48	"	13
							" "	15,093 "	"	"	"		49	5/6	16
							MST	19.7 days	"	"	"		3	0/6	56
			Ca-755	" " " " "		102	Tumor vol	428 mm³	"	"	"		46	8/8	7
							" "	14,104 "	"	"	"		93	"	13
							MST	23.8 days	"	"	"		31	2/8	65
			AKA-TOL	" " " " "		103	Tumor vol	1,068 mm³	"	5–9; 17–21	20		45	10/10	10
							" "	6,756 "	"	" "	"		71	"	26
							" "	8,889 "	"	" "	"		54	"	38
							MST	56.6 days	"	" "	"		2	0/10	99

APPENDIX III.—*Results of experimental studies in the Soviet Union with drugs developed there* [a] *(Continued)*

NSC No.	Compound	Drug vehicle	Tumor	Site and inoculum	Expt. No.	Parameter of effect	Controls	Treatment: Route	Treatment: Schedule, days	Doses, mg/kg/injection: Tested	Doses, mg/kg/injection: Optimal	Percent ILS or tumor inhibition	Survivors/total	Day of evaluation	ED50, μg/ml
183734	Palphicerin	Olive oil	S37	sc, 10^6 cells	104	Tumor vol	520 mm^3	sc	2–6	25		25	7/7	7	
						" "	2,827 "	"	"	"		79	"	13	
						" "	15,467 "	"	"	"		70	"	28	
						MST	56 days	"	"	"		7	2/7	80	
			S180	" 50 mg tumor susp	105	Tumor vol	1,081 mm^3	"	"	"		+11	10/10	7	
					106	" "	4,891 "	"	"	"		54	9/10	13	
						" "	16,220 "	"	"	"		+11	"	17	
						MST	30 days	"	"	"		0	0/10	56	
			RShM-5	" " " " "	815	Tumor vol	453 mm^3	"	"	25–50	25	40	8/8	7	
						" "	2,246 "	"	"	"	"	64	"	13	
						" "	5,084 "	"	"	"	"	63	"	19	
						" "	10,510 "	"	"	"	"	53	"	25	
						MST	42.9 days	"	"	"	"	9	1/8	65	
166100	Prospidine	Saline	L1210	ip, 10^5 cells	107, 108	MST	7 "	ip	1–5	200		0	0/15	7	
			La	" 0.2–0.3 ml tumor susp	109, 110 111	"	6–7 days	"	"	"		0	0/17	"	
			S-Jensen	sc, 0.3–0.4 ml tumor susp	112–118	Tumor wt	10.4–17.8 g	"	5–13	150–0.3		32–100	77/77	14	
			S45	"	119–125	" "	9.5–19.3 g	"	6–14	150–10		38–77	72/72	16	
			SM-1	"	126, 127	" "	4.8–25.2 g	"	5–13	150–100		52–71	22/22	14	
			S536	"	129	" "	23.8–30 g	"	6–14	100		51–53	20/20	16	
			Walker 256	"	130	" "	33 g	"	5–14	"		79	10/10	14	
			RS-1	"	131,133, 135	" "	10.7 g	"	9–19	120		79	6/10	21	
			S180	ip 0.2 ml ascitic fl	139–141	MST	6.5–12.5 days	"	1–5	200–100		30	0/31	7–14	
			S180	im, " " " "	142	Tumor wt	12 g	"	"	200		"	9/9	12	
			S180	sc, 0.3–0.4 ml tumor susp	136–138	" "	2.7–3.3 g	"	5–12	400–200		31–39	40/42	14	
			Ca-755	" 50 mg tumor susp	816	Tumor vol	122 mm^3	"	2–6	100–200	200	15	7/7	7	
						" "	2,846 "	"	"	"	"	75	"	11	
						" "	6,832 "	"	"	"	"	75	"	14	
						" "	18,922 "	"	"	"	"	83	"	18	
						MST	26.9 days	"	"	"	"	32	1/7	47	
				" " " " "	785	Tumor vol	604 mm^3	"	"	150–50	150	54	8/8	7	
						" "	6,642 "	"	"	"	"	67	"	13	
						" "	14,448 "	"	"	"	"	80	7/8	18	
			LL	" " " " "	786	" "	491 "	"	"	150–20	"	63	6/6	7	
						" "	2,987 "	"	"	"	"	82	"	13	
						" "	17,231 "	"	"	"	"	72	"	26	
						Tumor wt	12.4 g	"	"	"	"	31	5/6	36	
			AKATOL	" " " " "	787	Tumor vol	210 mm^3	"	"	100–150	"	81	6/6	7	
						" "	4,100 "	"	"	"	"	73	"	14	
						" "	12,807 "	"	"	"	"	59	"	22	
						" "	16,116 "	"	"	"	"	59	"	28	

									MST	32.7 days	"	"	"	"	9	0/6	54	
			PRZh	"	"	"	"	"	788	Tumor vol	5,964 mm³	"	"	150	73	7/7	7	
										" "	15,093 "	"	"	"	75	"	13	
										" "	27,111 "	"	"	"	81	"	23	
				"	"	"	"	"	788	MST	36 days	"	"	"	245	3/7	180	
			LL	"	"	"	"	"	817	Tumor vol	490 mm³	"	"	"	24	8/8	7	
										" "	2,231 "	"	"	"	36	"	11	
										" "	3,783 "	"	"	"	47	"	18	
										" "	7,177 "	"	"	"	34	"	25	
				"	"	"	"	"		MST	32 days	"	"	"	24			
				"	"	"	"	"		Tumor vol	2,654 mm³	"	"	"	47	9/9	8	
										" "	5,254 "	"	"	"	56	"	11	
										" "	10,540 "	"	"	"	51	"	18	
										" "	18,579 "	"	"	"	40	"	29	
										MST	36 days	"	"	"	18			
			AKA-TOL	"	"	"	"	"	818	Tumor vol	8,251 mm³	"	"	"	52	8/8	27	
										" "	3,927 "	"	"	"	51	"	13	
										MST	41 days	"	"	"	67			
			RShM-5	"	"	"	"	"	819	Tumor vol	856 mm³	"	"	"	38	"	7	
										" "	3,294 "	"	"	"	35	"	14	
										" "	15,412 "	"	"	"	58	6/8	27	
										MST	33 days	"	"	"	11			
			CaOv							[³H]dThd incl								> 1,000
			CaOv							NA content								> 500
			CaOv							Pro "								~ 200
216135	Fotrin	Saline	La	ip, 0.2–0.3 ml tumor susp					143–146	MST	7–8 days	ip	1–6	15–30	40–201	0/60	7–8	
			S-45	sc, 0.3–0.4 "					148–157	Tumor wt	14.2–18.6 g	"	6–12	30–7.5	28–91	156/156	16	
			SM-1	"		"			159–161	" "	11.6–14.7 g	"	5–13	15–10	43–56	32/32	15	
			LI0-1	im,0.2–0.3"					162–170	" "	2.8–2.9 g	"	1–8	20–30	32–84	64/64	11	
			S-37	sc, 0.3–0.4 "					173–176	" "	3.2–4.8 g	"	5–13	15–30	35–56	44/44	13	
			S180			"			177, 178	" "	5.1 g	"	" "	20–30	21–51	32/32	"	
			Ca-NK			"			179, 180	" "	3.6 g	"	" "	25	70	16/16	"	
			Ehrlich	ip, 0.2 ml ascitic fl					181–186	Ascites wt	Variable	"	1–7	20–30	49–100	64/64	8–10	
			Ca-755	sc, 50 mg tumor susp					789	Tumor vol	604 mm³	"	2–6	"	30	96	9/9	7
										" "	6,642 "	"	"	"	"	83	"	13
										" "	14,448 "	"	"	"	"	72	"	18
			LL	"	"	"	"	"	790	" "	491 "	"	"	20–75	20	51	6/6	7
										" "	2,987 "	"	"	"	"	72	"	13
										" "	8,653 "	"	"	"	"	63	"	19
										" "	17,231 "	"	"	"	"	56	"	26
167781	Diiodo-benzo-tepa	Boiled starch	S45	"	"	"	"	"	187–195	Tumor wt	[b]	Oral	5–14	20–80	60	100	10/10	15
			S-Jensen	"	"	"	"	"	196, 197	" "	[b]	"	5,7,9,11,13, 15,17,19	40–60	"	99.7	"	20
			SM-1	"	"	"	"	"	198, 199	" "	[b]	"	5–14	"	"	79	9/10	15
			S180	"	"	"	"	"	200, 202, 203	" "	[b]	"	"	40–80	40	99.2	10/10	"
			Ca-Guerin	"	"	"	"	"	204–206	" "	[b]	"	"	20–60	60	99.2	"	"

APPENDIX III.—*Results of experimental studies in the Soviet Union with drugs developed there* [a] *(Continued)*

NSC No.	Compound	Drug vehicle	Tumor	Site and inoculum	Expt. No.	Parameter of effect	Controls	Treatment Route	Treatment Schedule, days	Doses, mg/kg/injection Tested	Doses, mg/kg/injection Optimal	Percent ILS or tumor inhibition	Survivors/total	Day of evaluation	ED50, μg/ml
167781	Diiodobenzotepa	Boiled starch	Brown-Pierce epithelioma	it, 100 mg tumor susp	207–209	Extent and size of metastases		Oral	5–14	30–40	30	73	7/10	12	
148258	Ftorafur	Saline	L1210	ip, 10^6 cells	404, 405	MST	6.9 days	ip	2,6	250		16	0/6	16	
						"	8.3 "	"	" "	300–350	350	60	"	15	
		Tween-80 in water	L1210	" 10^5 "	406	"	9 "	"	1,5,9	50–833	500	80	"	17	
					407, 408, 409	"									
			P388	" " "	410	"	8 "	"	" " "	50–400		0	"	9	
			La	" 10^6 "	411, 412	"	6.2 "	"	1,5	200–600	600	85	"	12	
		Saline	La	" 5×10^6 cells	413, 414	"	8.8 "	"	" "	250–300	250	80	"	63	
			MOPC 406	" 50 mg tumor susp	415, 416	"	17 "	"	2,6	250		38	0/8	93	
			Ca-755	sc, " " " "	417–420	Tumor vol	344 mm^3	"	" "	200–300	300	76	8/8	7	
						" "	1,567 "	"	" "	"	"	84	"	13	
						" "	8,405 "	"	" "	"	"	63	"	19	
						MST	33.9 days	"	" "	"	"	2	0/8	63	
			AKA-TOL	" " " " "	421	Tumor vol	3,873 mm^3	"	" "	250	250	69	7/7	7	
						" "	8,334 "	"	" "	"	"	26	"	13	
						" "	17,149 "	"	" "	"	"	42	"	20	
						" "	21,826 "	"	" "	"	"	47	6/7	27	
						Tumor wt	7.6 g	"	" "	"	"	6	"	45	
		Saline	RShM-5	" " " " "	422	Tumor vol	64 mm^3	"	" "	300		+128	7/7	6	
						" "	856 "	"	" "	"		14	"	11	
						" "	12,628 "	"	" "	"		27	"	25	
						MST	36.9 days	"	" "	"		34	0/7	60	
			S37	sc, 10^6 cells	423	Tumor vol	348 mm^3	"	" "	"		86	8/8	7	
						" "	1,308 "	"	" "	"		37	"	14	
						" "	3,168 "	"	" "	"		18	"	23	
						MST	61 days	"	" "	"		2	0/8	91	
			LL	" 50 mg tumor susp	424, 425	Tumor vol	1,624 mm^3	"	" "	"		99	8/8	7	
						" "	10,870 "	"	" "	"		79	"	13	
						" "	22,611 "	"	" "	"		47	7/8	20	
						MST	24 days	"	" "	"		17	0/8	44	
		Tween-80 in water	S180	" " " " "	426, 427	Tumor wt	2.4 g	"	1–10	15–115	90	66	0/6	12	
			Mel. H.P.	" " " " "	428	" "	1.6 "	"	"	15–120	"	66	6/6	"	
			B16	" " " " "	429	MST	40 days	"	1,5.9	108–833		0	0/6	40	
			S-AK	" " " " "	430	Tumor wt	1.4 g	"	1–8	58–200	"	53	6/6	10	
			Ca-NK	" " " " "	431, 432	" "	1.8 "	"	1–6	115–200	200	68	"	8	
			Walker 256	" " " " "	433	" "	26.5 "	"	1–10	75–180	150	63	"	12	

		LS-Pliss 100	" 100 "	"	"	434	"	"	21.4 "	"	"	100–180	"	34	"	"	
		RS-1	"	"	"	435	"	"	6.9 "	"	"	"	"	65	"	"	
		S-Jensen	"	"	"	436	"	"	14.1 "	"	"	"	"	35	"	"	
		S45	"	"	"	437	"	"	6.8 "	"	2–12	"	"	0	"	15	
		S37					NA content										< 10
		L5178Y					"	"									50–10
		Ehrlich					"	"									50–10
		NK/Ly					"	"									< 10
		CaOv					[^{3}H]dThd incl										> 1,000
		CaOv					NA content										100
		CaOv					Pro	"									1,000
216134	Tomazin	Saline	S-AK	sc, 0.3–0.4 ml tumor susp		438–441	Tumor wt		4.2–7.6 g	"	3–12	50–100	75	50–60	41/47	13	
			S37	"	"	442–445	"	"	4.4–5.7 "	"	"	50–72.5	72.5	50–80	42/45	"	
			Ca-NK	"	"	446, 447	"	"	5.2–5.8 "	"	"	50–75		0	18/20	"	
			S180	"	"	448, 449	"	"	4.1–7.8 "	"	"	"	60	30–50	19/20	"	
			NK/Ly	iv, 0.2 ml ascitic fl		450, 451	Ascites wt		6.7 "	"	2–10	50	50	80	8/8	11	
									3.1 "	sc	3–11	20		0	5/5	12	
			Ehrlich	"	"	"	"	"	452	"	"	6.0 "	ip	4–10	50	"	70	10/10	11
									453	"	"	3.0 "	sc	1–8	"		0	7/8	10
			La	"	"	"	tumor susp		454, 455	MST		6 days	ip	1–5	37.5–75		0	0/20	6
			S-Jensen	sc, 0.3–0.4 ml tumor susp					456–460	Tumor wt		20–47 g	"	3–14	30–55	50	35–50	50/50	15
			SM-1		"				461	"	"	18.0 g	"	"	35	35	55	10/10	"
			S536		"				462–463	"	"	20–26 g	"	"	"	"	30	24/24	"
			RS-1		"				464	"	"	19 g	"	3–25	30		0	0/10	26
			AKA-TOL	"	50 mg tumor susp				791	Tumor vol		210 mm^3	"	2–6	50–75	50	68	6/6	7
										"	"	4,100 "	"	"	"	"	60	"	14
										"	"	12,807 "	"	"	"	"	38	"	22
										"	"	16,116 "	"	"	"	"	11	"	28
										MST		32.7 days	"	"	"	"	7	0/6	54
180024	Car-mino-mycin	Saline	L1210	ip, 10^5 cells					617	"		9.9 "	"	"	0.2		29	"	21
										"		9.9 "	"	2,6	0.5–0.6	0.6	38	"	"
			La	"	5 × 10^6 cells				618, 619	"		7.1 "	"	1–5	0.15		213	0/5	46
			MOPC 406	"	50 mg tumor susp				620	"		17 "	"	2,6	0.5		28	0/8	93
			LL	sc,	"	"	"	"	621	Tumor vol		1,624 mm^3	"	"	"	0.5		55	8/8	7
										"	"	10,870 "	"	"	"	"		17	7/8	13
										MST		24 days	"	"	"	"		21	0/8	44
			Ca-755	"	"	"	"	"	622	Tumor vol		421 mm^3	"	"	"	"		51	10/10	7
										"	"	12,488 "	"	"	"	"		34	9/10	15
										MST		24.2 days	"	"	"	"		24	0/10	41
			AKA-TOL	"	"	"	"	"	623	Tumor vol		466 mm^3	"	"	"	"		37	8/8	7
									624	"	"	1,930 "	"	"	"	"		49	"	13
				"	"	"	"	"	623, 624	"	"	4,139 "	"	"	"	"		50	6/8	20
			RShM-5	"	"	"	"	"	625	"	"	144 "	"	"	"	"		78	7/7	7
										"	"	1,116 "	"	"	"	"		+20	"	13
			PRZh	im,	"	"	"	"	626	"	"	6,732 "	"	"	"	0.6		40	8/8	7

APPENDIX III.—*Results of experimental studies in the Soviet Union with drugs developed there* [a] *(Continued)*

NSC No.	Compound	Drug vehicle	Tumor	Site and inoculum	Expt. No.	Parameter of effect	Controls	Treatment: Route	Treatment: Schedule, days	Doses, mg/kg/injection: Tested	Doses, mg/kg/injection: Optimal	Percent ILS or tumor inhibition	Survivors/total	Day of evaluation	ED50, μg/ml
180024	Carminomycin	Saline	PRZh	im, 50 mg tumor susp	626	Tumor vol	14,142 mm³	ip	2,6	0.6		32	7/8	14	
						" "	19,382 "	"	" "	"		+3	5/8	26	
						MST	50.4 days	"	" "	"		13	1/8	89	
			S37	sc, 10^6 cells	627	Tumor vol	348 mm³	"	" "	"		58	8/8	7	
						" "	1,308 "	"	" "	"		+30	"	14	
						" "	3,168 "	"	" "	"		+2	"	23	
						MST	61 days	"	" "	"		13	0/8	91	
			S180	" 50 mg tumor susp	628	Tumor vol	954 mm³	"	2–6	0.15		+33	6/6	7	
						" "	3,536 "	"	"	"		+64	"	14	
						" "	29,478 "	"	"	"		35	5/6	30	
			NK/Ly	ip, 7.5×10^6 cells	629–632	No. of ascitic cells/mouse	4.5×10^8	iv	1,3,5,7	1.34	1.5–2.0	54	38/40	9	
							"	"	" " " "	1.5	"	61	31/40	"	
							"	"	" " " "	1.66	"	37	30/40	"	
							"	"	" " " "	1.8	"	64	16/40	"	
							"	"	" " " "	1.9	"	75	12/40	"	
							"	"	" " " "	2.0	"	61	7/40	"	
			LI0-1	im, 0.2 ml tumor susp	633–637	Tumor wt	1.84 g	"	1,4 8	0.9	1.8	61	10/10	10	
				" " " " "	633–637	" "	" "	"	" " "	1.35	"	76	"	"	
						" "	" "	"	" " "	1.8	"	92	"	"	
						" "	" "	"	" " "	2.25	"	97	"	"	
						" "	1.94 "	Oral	1.4	2.75	3.75	71	"	"	
						" "	" "	"	" "	3.75	"	100	"	"	
			S180	sc, 10–20 mg tumor susp	638–643	" "	1.82 "	iv	3,8	2.0	2.5	66	"	"	
						" "	" "	"	" "	2.5	"	79	"	"	
						" "	" "	"	" "	3.2	"	84	8/10	"	
						" "	" "	"	" "	"	"	86	7/10	"	
						" "	" "	Oral	" "	2.5	5.0	7	10/10	"	
						" "	" "	"	" "	3.75	"	71	9/10	"	
						" "	" "	"	" "	5.0	"	89	8/10	"	
			S37			NA content									< 0.1
			L5178Y			" "									< 0.1
			Ehrlich			" "									< 0.1
			NK/Ly			" "									< 0.1
			CaOv			[³H]dThd incl									< 1
			CaOv			NA content									1
			CaOv			Pro "									3
76411	Olivomycin	5% Ethyl alcohol	LI0-1	im, 0.2 ml 2.5% cell susp	644	Tumor wt	2.18 g	iv	6,9,12,15	2.5		36	20/20	11	
					656	" "	" "	"	" " " "	3.75		54	"	"	
						" "	" "	"	" " " "	5.0		64	"	"	
						" "	" "	"	" " " "	6.25	6.25	80	19/20	"	
					657	" "	3.21 "	"	1,4,7	3.5		86	10/10	"	

		S180	sc, 10–20 mg tumor susp	658, 659	" "	1.9 "	"	3,5,7,9	"		45	15/15	10		
					" "	" "	"	" " " "	4.0		57	"	"		
					" "	" "	"	" " " "	5.0	5.0	61	14/15	"		
		La	ip, 0.3 ml tumor susp	820	MST	10 days	ip	1–9	2.0		74				
		La	ip, 10^6 cells	821	"	9.4 "	"	1,5	4–8	6.0	66	0/7	19		
		Ca-755	sc, 50 mg tumor susp	822	Tumor wt	5.1 g	"	4–14	1.0		0	8/8	17		
			" " " " "		MST	22.4 days	"	2–7	2.0		9				
			" " " " "		"	21.3 "	"	3–8	"		21				
					Tumor vol	785 mm^3	"	2,6	4–8	6.0	94	9/9	7		
					" "	10,836 "	"	" "	"	"	86	"	13		
					" "	20,580 "	"	" "	"	"	74	8/9	18		
					" "	23,873 "	"	" "	"	"	28	5/9	25		
					MST	34.6 days	"	" "	"	"	5	1/9	51		
	Saline	AKA-TOL	sc, 50 mg tumor susp	823	Tumor vol	780 mm^3	"	" "	"	4	70	7/7	7		
					" "	2,400 "	"	" "	"	"	49	"	13		
					" "	7,364 "	"	" "	"	"	3	"	20		
					" "	9,586 "	"	" "	"	"	2	"	26		
		S180	" " " " "	824	Tumor wt	5.2 g	"	2–14	1		8		"		
		S37			NA content								"	< 0.1	
		L5178Y			" "									1–0.1	
		Ehrlich			" "										
		NK/Ly			" "										
196869	Aton	Alcohol in saline	Ca-755	" " " " "	465–470	Tumor wt	5.1 g	"	2–12 3 ×/day	18		65	10/10	13	
		Poly-ethyl-ene oxide in citric acid		" " " " "	471, 472	" "	3.3 "	Oral	2–12 3 ×/day	40		51	7/8	"	
		Alcohol in saline	RShM-5	" " " " "	473	" "	1.8 "	ip	7–17 3 ×/day	18		45	7/7	22	
			KREBS-2	" " " " "	474	" "	2.7 "		5–15 3 ×/day	"		29	7/9	16	
		Poly-ethyl-ene oxide in citric acid	S91	" " " " "	475	" "	5.6 "	Oral	8–18	50		14	6/7	19	
		Alcohol in saline	S37			NA content								10–1	
			L5178Y			" "								1–0.1	
			Ehrlich			" "								0.1	
			NK/Ly			" "								1–0.1	

APPENDIX III.—*Results of experimental studies in the Soviet Union with drugs developed there* [a] *(Continued)*

NSC No.	Compound	Drug vehicle	Tumor	Site and inoculum	Expt. No.	Parameter of effect	Controls	Treatment: Route	Treatment: Schedule, days	Doses, mg/kg/injection: Tested	Doses, mg/kg/injection: Optimal	Percent ILS or tumor inhibition	Survivors/total	Day of evaluation	ED50, μg/ml
183737	Chanerol	Saline	L1210	ip, 10^6 cells	723	MST	8.5 days	ip	2–6	10	10	15	0/6	19	
			La	" " "	724	"	9.3 "	"	1–5	7		8	0/9	84	
			LL	sc, 50 mg tumor susp	725	Tumor vol	1,518 mm^3	"	2–6	10	"	65	6/6	7	
						" "	11,514 "	"	"	"	"	54	"	13	
						" "	15,093 "	"	"	"	"	43	"	16	
						MST	19.7 days	"	"	"	"	7	0/6	35	
						Tumor vol	1,518 mm^3	"	2,6	20		37	6/6	7	
						" "	11,514 "	"	" "	"		32	"	13	
						" "	15,093 "	"	" "	"		25	5/6	16	
			LL	" " " " "	725	MST	19.7 days	"	" "	"		5	0/6	35	
			Ca-755	" " " " "	726–728	Tumor vol	443 mm^3	"	2–6	10	"	97	6/6	7	
						" "	5,549 "	"	"	"	"	82	"	13	
						" "	11,007 "	"	"	"	"	62	"	17	
						MST	22.3 days	"	"	"	"	42	0/6	39	
				" " " " "	729	Tumor vol	619 mm^3	"	2,6	20–40	40	92	8/8	7	
						" "	7,370 "	"	" "	"	"	65	"	14	
						" "	11,868 "	"	" "	"	"	33	"	17	
						MST	27.8 days	"	" "	"	"	9	0/8	43	
			AKA-TOL	" " " " "	730–733	Tumor vol	622 mm^3	"	2–6	10		81	7/7	7	
						" "	3,242 "	"	"	"		65	"	14	
						" "	7,057 "	"	"	"		59	"	20	
						" "	8,166 "	"	"	"		28	"	26	
						" "	10,010 "	"	"	"		4	"	33	
			RShM-5	" " " " "	734–737	Tumor vol	270 mm^3	"	"	"		71	6/7	7	
						" "	1,429 "	"	"	"		33	"	13	
						" "	3,863 "	"	"	"		17	"	20	
						MST	39.1 days	"	"	"		19	0/7	68	
						Tumor vol	270 mm^3	"	2,6	20		94	7/7	7	
						" "	1,429 "	"	" "	"		14	"	13	
						" "	3,863 "	"	" "	"		+4	6/7	20	
						MST	39.1 days	"	" "	"		8	0/7	68	
			PRZh	im, " " " "	738	Tumor vol	12.8 mm^3	"	1–5	8		63	7/7	7	
						" "	16.2 "	"	"	"		43	"	13	
						" "	18.5 "	"	"	"		62	"	19	
						Tumor wt	5.3 g	"	"	"		38	"	22	
			S37	sc, 10^6 cells	739	Tumor vol	1,173 mm^3	"	2–6	10		75	5/7	7	
						" "	2,195 "	"	"	"		+5	"	13	
						" "	2,307 "	"	"	"		+48	"	17	
			S180	" 50 mg tumor susp	740	" "	954 "	"	"	"		24	6/6	7	
						" "	3,536 "	"	"	"		+26	"	14	
						" "	11,676 "	"	"	"		+7	"	21	
			S37			NA content									50–20
			L5178			" "									50–20
			Ehrlich			" "									100–50
			NK/Ly			" "									< 50

			CaOv			[^{3}H]dThd incl									70
			CaOv			NA content									40
			CaOv			Pro "									60
183738	Colchi-zin	Saline	L1210	ip, 10^6 cells	709	MST	8.5 days	"	2,6	25–400	100	0	0/3	69	
			P388	" " "	710	"	9.6 "	"	1–8	120		157	0/7	20	
			La	" " "	711	"	9.3 "	"	1–5	"		335	1/9	84	
					712	"	17.4 "	"	"	110		32	0/8	52	
			MOPC 406	50 mg tumor susp	713	"	14.7 "	"	2–6	120		34	0/6	37	
			LL	sc, 50 mg tumor susp	714	Tumor vol	1,554 mm^3	"	"	"		18	6/6	7	
						" "	11,764 "	"	"	"		17	"	13	
						" "	21,268 "	"	"	"		0	"	21	
						MST	24.1 days	"	"	"		7	0/6	35	
						Tumor vol	1,554 mm^3	"	2,6	170		17	6/6	7	
						" "	11,764 "	"	" "	"		16	"	13	
						" "	21,268 "	"	" "	"		+7	2/6	21	
						MST	24.1 days	"	" "	"		8	0/6	35	
			Ca-755	" " " " "	715, 716	Tumor vol	785 mm^3	"	2–6	120		70	6/6	7	
						" "	7,519 "	"	"	"		+12	4/6	13	
						" "	12,252 "	"	"	"		+6	3/6	17	
						MST	23.7 days	"	"	"		12	1/6	33	
						Tumor vol	341 mm^3	"	2,6	85–170	170	95	6/6	7	
						" "	5,401 "	"	" "	"	"	54	"	13	
						" "	19,153 "	"	" "	"	"	+19	5/6	22	
						MST	26.1 days	"	" "	"	"	3	0/6	45	
			AKA-TOL	" " " " "	717	Tumor vol	393 mm^3	"	" "	100		84	10/10	7	
						" "	8,109 "	"	" "	"		66	"	13	
						" "	21,954 "	"	" "	"		19	"	22	
						MST	33.1 days	"	" "	"		6	0/10	106	
			RShM-5	" " " " "	718	Tumor vol	111 mm^3	"	2–6	120		64	7/8	7	
						" "	1,124 "	"	"	"		12	"	14	
						" "	6,689 "	"	"	"		+18	6/8	23	
						" "	17,531 "	"	"	"		+22	4/8	32	
						MST	39.1 days	"	"	"		18	0/8	62	
						Tumor vol	111 mm^3	"	2,6	170		59	8/8	7	
						" "	1,124 "	"	" "	"		31	7/8	14	
						" "	6,689 "	"	" "	"		+21	6/8	23	
						" "	17,531 "	"	" "	"		0	4/8	32	
						MST	39.1 days	"	" "	"		21	0/8	62	
			PRZh	" " " " "	719	Tumor vol	2,937 mm^3	"	2–6	100		45	8/8	7	
						" "	7,230 "	"	"	"		72	"	13	
						" "	9,032 "	"	"	"		49	"	20	
						MST	8.8 days	"	"	"		35	0/8	28	
			S37	sc, 10^6 cells	720	Tumor vol	321 mm^3	"	"	120		53	6/6	7	
						" "	777 "	"	"	"		54	"	13	
						" "	3,230 "	"	"	"		48	"	19	
						" "	11,199 "	"	"	"		40	"	30	
						MST	52.4 days	"	"	"		15	0/6	90	

APPENDIX III.—*Results of experimental studies in the Soviet Union with drugs developed there* [a] *(Continued)*

NSC No.	Compound	Drug vehicle	Tumor	Site and inoculum	Expt. No.	Parameter of effect	Controls	Treatment: Route	Treatment: Schedule, days	Doses, mg/kg/injection: Tested	Doses, mg/kg/injection: Optimal	Percent ILS or tumor inhibition	Survivors/total	Day of evaluation	ED50, μg/ml
183738	Colchizin	Saline	S180	sc, 50 mg tumor susp	721	Tumor vol	1,081 mm^3	ip	2–6	100		+72	11/11	7	
						" "	4,891 "	"	"	"		+44	"	13	
						MST	30 days	"	"	"		19	0/11	56	
			S37			NA content									50–20
			L5178Y			" "									10
			Ehrlich			" "									50–20
			NK/Ly			" "									100–50
271276	Diazan	Saline	L1210	ip, 10^5 cells	210	MST	8.4 ± 0.2 days	sc	1,3,5,7	15	15	103	2/10	30	
					211	"	" " " "	"	" " " "	2	"	10	0/10	"	
					212	"	" " " "	"	1,5,10	150	"	60	"	"	
					213	"	" " " "	"	" " "	200	"	30	"	"	
					214	"	" " " "	"	1,3.5,7	10	"	"	"	"	
					215	"	" " " "	"	" " " "	5	"	7	"	"	
					216	"	" " " "	"	1	100	"	10	"	"	
					217	"	" " " "	"	"	130	"	12	"	"	
					218	"	" " " "	"	"	150	"	17	"	"	
			P388	" 10^6 "	219	"	9.8 ± 0.2 "	"	1,3,5,7,9, 11,13,15	25	25	73	"	"	
					220	"	" " " "	"	1,4,7,10,13	"	"	52	"	"	
					221	"	" " " "	"	1,3,5.7 9, 11,13,15, 17,19	"	"	128	"	"	
					222	"	" " " "	"	1,4,7,10	150	"	85	"	"	
					223	"	" " " "	"	1,5,9,13	"	"	76	"	"	
					224	"	" " " "	"	1,6,11	"	"	66	"	"	
					225	"	" " " "	"	1,6,11,16	"	"	90	0/6	"	
					226	"	" " " "	ip	1,3,5	25	"	59	"	"	
					227	"	" " " "	"	1,5,9	75	"	58	"	"	
					228	"	" " " "	"	2	150	"	17	"	"	
					229	"	" " " "	"	1.6	"	"	76	"	"	
					230	"	" " " "	"	1,5,9	"	"	52	"	"	
			La	" 10^8 "	231	"	6.5 ± 0.14 days	"	0,2,4.6,8	20	20	244	3/10	20	
					232	"	" " " "	"	1,3,5,7,9	"	"	120	1/10	"	
					233	"	" " " "	"	2,4,6,8,10	"	"	115	"	"	
					234	"	" " " "	"	0.5,10,15	150	"	140	"	"	
			Ca-755	sc, 0.3 ml tumor susp	235	Tumor wt	1.7 g	"	1,4,7 10,13	20		70	0/10	14	
						" "	" "	"	7,10,13	25		29	"	"	
			Walker 256	" " " " "	236	" "	16.9 "	"	1,4,7,9	15		95	"	10	
			S45	" 0.6 " " "	237, 238	" "	19.4 "	"	5,7,9,11,13	4		90.5	"	14	
						" "	" "	"	" " " " "	5		94	"	"	
						" "	" "	"	7,10,13	"		64	"	"	
			Mel. H.P.	" 0.3 " " "	239	" "	3.3 "	"	14,16,18	40		51	"	19	

		Saline	Ca-Jensen	" " " " "	240	" "	15.2	"	"	5,7,9,11,13	5		71	"	14
269146	Varia-mycin	Saline	L1210	ip, 10^5 cells	660	MST	10.8	days	"	1–6	0.25–1.0		0	"	12
						"	"	"	iv	1,4,7	1.0–2.0		"	"	"
			P388	" " "	661	"	13.2	"	ip	1–6	0.12–1.25	1.0	95	3/10	30
						"	"	"	iv	1,3,5,7	1.0–1.5	"	8	0/10	"
			La	ip, 0.5 ml cell susp	662	"	11.4	"	ip	1–6	0.5–0.75	0.75	61	2/10	"
						"	"	"	iv	1,4,7	1.0–1.5		23	5/10	"
			LI0-1	sc, 20 mg cell susp	663	Tumor vol	6,700	mm^3	ip	1–9	0.15–0.5	0.15	61	10/10	14
				" " " " "		" "	"	"	iv	1,3,5,7,9	0.25–0.75	0.5	51	9/10	"
			Ca-755	" " " " "	664	" "	6,300	"	ip	1–9	0.15–0.5	0.15	69	"	12
						" "	"	"	iv	1,3,5,7,9	0.25–0.75	0.25	71	10/10	"
			S37	ip, 5×10^6 cells	665	" "	5,100	"	ip	1–8	0.1–0.3	0.15	67	9/10	10
						" "	"	"	"	3–7	"	"	60	"	"
						" "	"	"	iv	1,3,5,7,9	0.15–0.5	0.25	65	8/10	"
			Ehrlich	" " "	666	" "	5,800	"	ip	1–8	0.1–0.25	0.15	21	9/10	"
						" "	"	"	iv	1,3,5,7,9	0.15–0.5	0.25	31	8/10	"
			S180	" " "	667	" "	4,300	"	ip	1–9	"	0.15	51	10/10	"
						" "	"	"	iv	3,5,7,9	0.25–0.75	0.5	44	9/10	"
			Mel. H.P.	sc, 20 mg tumor susp	668	" "	5,400	"	ip	9–17	0.15–0.5	0.25	72.3	10/10	21
						" "	"	"	"	14–20	"	"	37	9/10	"
						" "	"	"	iv	9,11,13, 15,17	0.25–0.75	"	41	10/10	"
						" "	"	"	"	14,16,18.20	"	0.5	36	8/10	"
			Walker 256	sc, 30-mm^3 tumor frag	669	" "	37,000	"	ip	3–7	0.2–0.4	0.2	69	10/10	9
						" "	"	"	iv	3,5,7	0.4–0.8	0.4	34	9/10	"
			S45	" " " " "	670	" "	35,900	"	ip	3–11	0.2–0.4	0.2	70	10/10	14
						" "	"	"	iv	3,7,9,11	0.4–0.8	0.4	72	"	"
			SM-1	" " " " "	671	" "	43,100	"	ip	10–18	0.2–0.4	0.2	56	"	20
						" "	"	"	iv	10,12,14, 16,18	0.4–0.8	0.5	70	9/10	"
			Ca Guerin	sc, tumor frag	672	" "	41,600	"	ip	10–18	0.2–0.4	0.3	63	10/10	19
						" "	"	"	iv	10 12,14, 16,18	0.4–0.8	0.4	34	"	"
			Hep-2 primary culture of human tumor												2×10^{-3}
			Hep-2 primary culture of human tumor												5×10^{-3}

APPENDIX III.—*Results of experimental studies in the Soviet Union with drugs developed there* [a] *(Continued)*

NSC No.	Compound	Drug vehicle	Tumor	Site and inoculum	Expt. No.	Parameter of effect	Controls	Treatment Route	Treatment Schedule, days	Doses, mg/kg/injection Tested	Doses, mg/kg/injection Optimal	Percent ILS or tumor inhibition	Survivors/total	Day of evaluation	ED50, ug/ml
269146	Variamycin	Saline	Hep-2 primary culture of human tumor												1×10^{-4}
			Hep-2 primary culture of human tumor												5×10^{-4}
99773	Reumycin	Saline	L5178Y	ip, 5×10^{6} cells	45	Tumor vol	6,800 mm^3	ip	1–9	1.0–2.5	1.5	65	9/10	12	
						" "	" "	iv	1,3,5,7,9	1.5–5.0	2.5	55	"	"	
			S37	" " "	44	" "	7,200 "	ip	1–9	0.25–1.0		31	8/10	"	
						" "	" "	iv	1,3,5,7,9	1.5–5.0	"	50	9/10	"	
			Ehrlich	" " "	81	" "	5,000 "	ip	1–9	0.25–1.0	0.25	"	8/10	10	
						" "	" "	iv	1,3,5,7,9	1.0–2.5	1.5	57	9/10	"	
			Ca-755	sc, 50 mg tumor susp	46	" "	6,700 "	ip	1–9	"	"	61	10/10	12	
						" "	" "	iv	1,3,5,7,9	1.5–3.5	2.5	47		"	
						" "	" "	Oral	1–9	25–75	50	"	9/10	"	
			Mel. H.P.	" 20 " " "	158	" "	5,640 "	ip	1–9	1.0–2.5	1.5	54	"	14	
						" "	" "	iv	1,3,5,7,9	1.5–3.5	2.5	45	10/10	"	
						" "	" "	Oral	1–9	25–75	50	55	"	"	
			B16	" " " " "	201	MST	21.2 days	ip	1–9	1.0–2.5		11		25	
						"	" "	iv	1,3,5,7,9	1.5–3.5		15		"	
			S180	" 3 × 3-mm tumor frag	171	Tumor vol	2,015 mm^3	ip	1–9	1.0–2.5	1.5	40	"	12	
						" "	" "	iv	1,3,5,7,9	1.5–3.5	2.5	35	9/10	"	
						" "	" "	Oral	1–9	25–50	50	29	10/10	"	
			LL	im, 20 mg tumor susp	172	" "	5,020 "	ip	1–9	0.5–2.0	1.5	20	"	"	
						" "	" "	iv	1,3,5,7,9	1.5–3.5	2.5	14	"	"	
			L1210	ip, 10^5 cells	147	MST	10 days	ip	1–9	0.5–2.5		10.3	0/10	"	
			P388	" " "	132	"	11.6 days	"	"	"		11	"	30	
			Walker 256	sc, 30-mm^3 tumor frag	57	Tumor vol	44,000 mm^3	"	3–6	5–10	10	35	9/10	9	
						" "	" "	iv	3,5,7	5–20	"	39.5	"	"	
			Ca-Guerin Hep–2	" " " " "	34	" "	30,600 "	ip	9–13	5–10		30	10/10	19	
						" "	" "	Oral	9–18	50–70		25	"	"	
															0.25–0.3
275653	Agavoside	Saline	L1210	ip, 10^6 cells	682	MST	8.4 days	ip	1–5	4–8	5	12	0/7	13	
			LL	sc, 50 mg tumor susp	683	Tumor vol	2,577 mm^3	"	3–7	5–7	7	67	7/7	"	

								" "	8,924 "	"	"	"	"	58	6/7	19
								Tumor wt	7.7 g	"	"	"	"	55	"	"
			Ca-755	"	"	"	"	684	Tumor vol	692 mm^3	"	2–6	6–7	6	71	9/9	7
									" "	8,711 "	"	"	"	"	52	7/9	13
									" "	17,466 "	"	"	"	"	10	"	18
									MST	25.5 days	"	"	"	"	12	0/9	40
			AKA-TOL	"	"	"	"	685	Tumor vol	908 mm^3	"	2–9	5–6	5	33	7/7	7
									" "	2,650 "	"	"	"	"	63	6/7	13
									Tumor wt	2 g	"	"	"	"	30	5/7	17
			RShM-5	"	"	"	"	686	Tumor vol	576 mm^3	"	3–7	5–7	"	60	8/8	8
									" "	2,857 "	"	"	"	"	50	7/8	14
									" "	9,448 "	"	"	"	"	47	"	20
									" "	9,648 "	"	"	"	"	14	"	21
									Tumor wt	6 g	"	"	"	"	15	"	23
			PRZh	im,	"	"	"	"	687	Tumor vol	802 mm^3	"	2–6	"	7	72	7/7	13
									" "	4,427 "	"	"	"	"	66	6/7	20
									Tumor wt	3.7 g	"	"	"	"	54	"	21
			B16	sc,	"	"	"	"	688	Tumor vol	845 mm^3	"	"	8		60	7/7	8
									" "	6,026 "	"	"	"			36	"	14
									" "	16,370 "	"	"	"			34	6/7	20
									Tumor wt	12.6 g	"	"	"			16	"	21
			S37							NA content								50–10
			L5178Y							" "								"
			Ehrlich							" "								"
			NK/Ly							" "								"
23471	Digi-tonin	Saline	L1210	ip, 10^6 cells				673	MST	9 days	"	1–7	6		0	0/8	11	
			P388	" 10^7 "				674	"	11.5 "	"	1–5	15		12	"	15	
			La	" " "				675	"	16 "	"	1–10 (q other day)	"		24	"	60	
								676	"	17.2 "	"	1–5	10		214	1/8	150	
			LL	sc, 50 mg tumor susp				677	Tumor vol	763 mm^3	"	2–6	10–20	20	44	8/8	7	
									" "	6,024 "	"	"	"	"	+54	"	13	
									" "	10,895 "	"	"	"	"	+1	"	10	
									Tumor wt	6.6 g	"	"	"	"	17	"	19	
			Ca-755	"	"	"	"	678	Tumor vol	667 mm^3	"	3–7	"	"	69	"	8	
									" "	5,210 "	"	"	"	"	21	"	14	
									" "	8,716 "	"	"	"	"	+20	"	17	
									Tumor wt	9.5 g	"	"	"	"	"	7/8	19	
			B16	"	"	"	"	679	Tumor vol	1,992 mm^3	"	4–8	20–25	"	60	8/8	10	
									" "	7,059 "	"	"	"	"	19	3/8	19	
			RShM-5	"	"	"	"	680	" "	458 "	"	3–7	10–15	15	51	8/8	7	
									" "	1,046 "	"	"	"	"	35	"	13	
									" "	3,258 "	"	"	"	"	0	"	19	
									" "	6,834 "	"	"	"	"	+24	"	25	
									Tumor wt	5.3 g	"	"	"	"	+13	6/8	26	
			S37	"	10^7 cells			681	Tumor vol	826 mm^3	"	"	20		47	7/8	7	
									" "	1,919 "	"	"	"		45	"	13	
									" "	12,367 "	"	"	"		55	"	25	
									" "	21,787 "	"	"	"		33	"	30	

APPENDIX III.—*Results of experimental studies in the Soviet Union with drugs developed there* [a] *(Continued)*

NSC No.	Compound	Drug vehicle	Tumor	Site and inoculum	Expt. No.	Parameter of effect	Controls	Treatment: Route	Treatment: Schedule, days	Doses, mg/kg/injection: Tested	Doses, mg/kg/injection: Optimal	Percent ILS or tumor inhibition	Survivors/total	Day of evaluation	ED50, μg/ml
23471	Digitonin	Saline	S37			NA content									100–50
			L5178Y			" "									"
			Ehrlich			" "									"
			NK/Ly			" "									50–10
275654	Funkioside	Saline	La	ip, 10^7 cells	689	MST	17.2 days	ip	1–5	10–20	10	88	0/8	96	
			LL	sc, 50 mg tumor susp	690	Tumor vol	1,210 mm^3	"	3–7	6–20	6	77	8/8	7	
						" "	6,879 "	"	"	"	"	68	"	13	
						Tumor wt	7.3 g	"	"	"	"	57	"	15	
			Ca-755	" " " " "	691	Tumor vol	666 mm^3	"	"	7–25	7	70	"	7	
						" "	5,210 "	"	"	"	"	48	"	13	
						" "	8,716 "	"	"	"	"	5	"	19	
						Tumor wt	9.5 g	"	"	"	"	+4	7/8	21	
					692	Tumor vol	5,075 mm^3	"	4–8	10		66	8/8	10	
						" "	22,657 "	"	"	"		50	"	17	
						" "	23,518 "	"	"	"		36	"	21	
			AKA-TOL	" " " " "	693	" "	797 "	"	2–6	7		55	"	7	
						" "	3,700 "	"	"	"		73	"	12	
						" "	12,136 "	"	"	"		70	5/8	18	
				" " " " "	694	" "	797 "	iv	"	"		69	8/8	7	
						" "	3,700 "	"	"	"		71	"	12	
						" "	12,136 "	"	"	"		80	"	18	
						" "	22,641 "	"	"	"		70	"	24	
						" "	23,436 "	"	"	"		53	"	28	
						MST	32 days	"	"	"		16	1/8	40	
			RShM-5	" " " " "	695	Tumor vol	576 mm^3	ip	3–7	5–20	20	63	8/8	8	
						" "	2,857 "	"	"	"	"	"	"	14	
						" "	9,448 "	"	"	"	"	62	"	18	
						" "	9,648 "	"	"	"	"	57	"	21	
						Tumor wt	6 g	"	"	"	"	47	"	"	
			B16	" " " " "	696	Tumor vol	1,992 mm^3	"	4–8	20		71	6/8	10	
						" "	7,059 "	"	"	"		52	"	17	
						Tumor wt	7.7 g	"	"	"		38	"	20	
			S37	sc, 10^7 cells	697	Tumor vol	825 mm^3	"	3–7	8–20	"	61	8/8	8	
						" "	1,919 "	"	"	"	"	28	"	13	
						" "	4,345 "	"	"	"	"	20	"	17	
						" "	12,367 "	"	"	"	"	37	"	24	
			S37			NA content									50–10
			L5178Y			" "									10
			Ehrlich			" "									50–10
			NK/Ly			" "									10
275655	Vitalboside	Saline	L1210	ip, 10^6 cells	698	MST	10 days	"	2–6 (q other day)	6–12	12	3	0/8	10	
			P388	" 10^7 "	699	"	10.7 "	"	2–6	6–14	10	0	3/8	11	

			La	" " "	700	"	16 "	"	1–10 (q other day)	6–12	"	134	1/9	76		
			LL	sc, 50 mg tumor susp	701	Tumor vol	1,219 mm³	"	2–6	8–14	14	24	8/8	7		
						" "	6,006 "	"	"	"	"	13	7/8	11		
						" "	10,455 "	"	"	"	"	23	"	16		
						" "	18,230 "	"	"	"	"	11	"	22		
						Tumor wt	10.2 g	"	"	"	"	0	"	23		
				" " " " "	702	Tumor vol	1,219 mm³	"	"	14		40	8/8	7		
						" "	6,006 "	"	"	"		15	7/8	11		
						" "	10,455 "	"	"	"		22	"	16		
						" "	18,230 "	"	"	"		10	"	22		
						Tumor wt	10.2 g	"	"	"		0	"	23		
			Ca-755	" " " " "	703	Tumor vol	725 mm³	"	"	8–15	15	75	"	7		
						" "	6,739 "	"	"	"	"	46	"	12		
						" "	14,783 "	"	"	"	"	24	"	17		
						Tumor wt	9.8 g	"	"	"	"	10	"	"		
			AKA-TOL	" " " " "	704	Tumor vol	661 mm³	"	"	10		36	8/8	7		
						" "	4,921 "	"	"	"		6	"	13		
						" "	13,207 "	"	"	"		15	7/8	20		
						Tumor wt	7.9 g	"	"	"		0	"	"		
				" " " " "	705	Tumor vol	1,215 mm³	"	"	14		72	6/8	7		
						" "	3,177 "	"	"	"		44	"	12		
						" "	9,743 "	"	"	"		0	"	18		
						Tumor wt	7.5 g	"	"	"		"	"	25		
			B16	" " " " "	706	Tumor vol	2,226 mm³	"	3–7	8–14	10	65	8/8	8		
						" "	5,196 "	"	"	"	"	21	"	14		
				" " " " "	707	" "	622 "	iv	2–6	10–14	14	70	7/8	7		
						" "	12,018 "	"	"	"	"	48	"	13		
						" "	12,291 "	"	"	"	"	34	"	17		
						Tumor wt	13.2 g	"	"	"	"	23	"	20		
			S37	sc, 10^7 cells	708	Tumor vol	325 mm³	ip	4–8	8–20	8	81	7/7	8		
						" "	1,044 "	"	"	"	"	76	"	12		
						" "	2,977 "	"	"	"	"	70	"	19		
						Tumor wt	5.1 g	"	"	"	"	65	"	25		
			S37			NA content									50–10	
			L5178Y			" "									"	
			Ehrlich			" "									"	
			NK/Ly			" "									"	
275652	Gluco-man-nan	Saline	L1210	ip, 10^6 cells	741	MST	8.2 days	"	1–5	5–10		0		12		
			P388	" " "	742	"	10.4 "	"	"	10		"		"		
			LL	sc, 50 mg tumor susp	743	Tumor wt	2 g	"	2–11	"	10	80	10/10	"		
				" " " " "	744	" "	2 "	Oral	"	100, 400	100	50	"	"		
			Ca-755	" " " " "	745	" "	2.31 "	ip	2–7	10, 100, 200, 400	10	43	"	19		
						" "	2.31 "	Oral	"	400	400	71	"	"		
			AKA-TOL	" " " " "	746	Tumor vol	9,418 mm³	ip	"	10	10	66	"	18		
			RShM-5	" " " " "	747	" "	413 "	"	2–11	100	100	68	"	14		
			PRZh	" " " " "	748	Tumor wt	3.42 g	"	2–7	10		0	"	"		

APPENDIX III.—*Results of experimental studies in the Soviet Union with drugs developed there* [a] *(Continued)*

NSC No.	Compound	Drug vehicle	Tumor	Site and inoculum	Expt. No.	Parameter of effect	Controls	Treatment: Route	Treatment: Schedule, days	Doses, mg/kg/injection: Tested	Doses, mg/kg/injection: Optimal	Percent ILS or tumor inhibition	Survivors/total	Day of evaluation	ED50, µg/ml
275652	Glucomannan	Saline	S37	sc, 50 mg tumor susp	749	Tumor wt	3.26 g	ip	5–19	10		21	8/8	20	
						" "	1.6 "	"	"	50		0	10/10	"	
						" "	3.26 "	Oral	"	400		"	8/8	"	
			S180	" " " " "	752	" "	5.7 "	ip	"	10		"	"	"	
						" "	" "	Oral	"	100	100	52	10/10	"	
275656	Dioxadet	Saline	S37	ip, 0.1 ml ascitic fl	255	Vol ascitic fl, dense prec	4.5–1.21 ml	ip	2–10	1.5		99.1–100	9/10	11	
		10% Ethyl alcohol			256	Vol ascitic fl, dense prec	4.02–1.3 "	"	"	"		22.8–32	"		
		Saline	S37	" " " " "	257	Vol ascitic fl, dense prec	2.75–0.82 "	"	2–7	"		80–95	10/10	8	
					258	Vol ascitic fl, dense prec	3.23–1.3 "	"	"	"		29–34	"		
			NK/Ly	" " " " "	259	Vol ascitic fl, dense prec	6.47–1.89 "	sc	2–12	"		43.3–63.4	"	13	
					260	Vol ascitic fl, dense prec	5.01–1.33 "	ip	"	"		100	9/10		
			Ehrlich	" " " " "	261	Vol ascitic fl, dense prec	5.08–1.37 "	"	2–9	"		"	10/10		
			L1210	ip, 10^5 cells	262	MST	7.71 days	"	2–7	"		33–133	1/6	60	
			OYa	ip, 0.4 ml ascitic fl	263	Vol ascitic fl	4.45 ml	"	2–9	0.6		85	9/10	10	
				" " " " "	264	" " "	4.33 "	sc	"	"		29	10/10	"	
		10%		" " " " "	265	" " "	27.2 "	"	2–10	0.4		16	"	11	
		Ethyl alcohol		" " " " "	266	" " "	23.1 "	ip	"	"		81	"	"	
		Saline	S37	sc, 0.1 " " "	267	Tumor wt	1,151 mg	"	4–16	0.5		15.2	"	19	
						" "	" "	"	"	1.0	1.5–2.0	39.6	"	"	
						" "	" "	"	"	1.5		52.2	"	"	
						" "	" "	"	"	2.0		54.6	"	"	
						" "	" "	"	"	2.5		67.0	3/10	"	
				" " " " "	268	" "	1,740 "	"	4–15	1.5		86	10/10	16	
		10%		" " " " "	269	" "	1,100 "	"	"	"		72.7	15/15	"	
		Ethyl		" " " " "	270	" "	1,247 "	"	"	"		50.2		"	
		alcohol		" " " " "		" "	" "	"	6,8,10, 12,14	3.0		79.3			

			" " " " "			" "	" "	"	4,7,10,13	4.5		82.2		
	Saline	Ehrlich	" " " " "		271	" "	2,830 "	"	7–17	2.0		54.0	11/14	18
			" " " " "		272	" "	2,380 "	"	6–16	"		55	10/10	17
						" "	" "	"	"	1.5		41	"	
						" "	" "	"	"	1.0		36	"	
		S180	sc, 0.2 ml 30% tumor susp		273	" "	3,530 "	"	6–17	1.7		37	"	18
			"	"	274	" "	2,250 "	"	6–15	2.0		48	14/14	16
		LI0-1	ip, 0.1	"	275	" "	2,850 "	"	"	"		40	"	"
		Walker 256	sc, 0.2	"	276	" "	30,720 "	"	5–16	0.3		74	10/10	17
						" "	" "	"	"	0.4		99.8	"	
						" "	" "	"	"	0.5	0.4–0.5	99.7	"	
						" "	" "	"	"	0.6		100	9/10	
						" "	" "	"	"	0.7		"	6/10	
			" "	"	277	" "	32,306 "	"	5–10	0.5		99.6	10/10	"
		S45	" 0.6	"	278	" "	8,132 "	"	5–13	0.4		77.7	"	14
	10% Ethyl alcohol		" "	"	279	" "	10,135 "	"	4–16	0.5		93.9	"	17
	Saline	Ca-Jensen	" 0.4	"	280	" "	31,210 "	"	6–18	0.4		88.7	8/10	19
				"	281	" "	32,870 "	"	3–16	0.5		99.3	9/10	17
	10% Ethyl alcohol	MOPC 406		"	282	" "	19,596 "	"	3–14	"		99.7	11/11	15
	Tributyric iodine–lipoic alcohol		" "	"	283	" "	16,450 "	im	5–10	2.0		100.0	6/6	"
	Saline	LS-Pliss		"	284	" "	16,000 "	ip	4–14	0.5		20.0	10/10	"
	10% Ethyl alcohol	LS-Pliss		"	285	" "	25,300 "	"	"	"		39.0	"	14
		S37				NA content								50–10
		L5178Y				" "								< 10
		Ehrlich				" "								"
		NK/Ly				" "								"
275568	Phenthyrine	Boiled starch	L1210	ip, 10^6 cells	51	MST	7.6 days	Oral	2,6	200		5	0/6	13
			La	ip, 3.5×10^6 cells	52	"	11.2 "	"	1–5	60		7	"	61
			MOPC 406	ip, 50 mg tumor susp	53	"	14.7 "	"	2–6	"		14	"	37
						"	" "	"	2,6	150		18	"	"
			LL	sc, 50 mg tumor susp	54	Tumor vol	3,786 mm^3	"	2–6	60		26	7/7	9
						" "	6,300 "	"	"	"		"	"	13
						" "	11,234 "	"	"	"		28	"	21
						MST	27.8 days	"	"	"		29	1/7	40

APPENDIX III.—*Results of experimental studies in the Soviet Union with drugs developed there* [a] *(Continued)*

NSC No.	Compound	Drug vehicle	Tumor	Site and inoculum	Expt. No.	Parameter of effect	Controls	Treatment: Route	Treatment: Schedule, days	Doses, mg/kg/injection: Tested	Doses, mg/kg/injection: Optimal	Percent ILS or tumor inhibition	Survivors/total	Day of evaluation	ED50, μg/ml
275568	Phenthyrine	Boiled starch	Ca-755	sc, 50 mg tumor susp	55	Tumor vol	403 mm³	Oral	2,6	200		97	8/8	7	
						" "	8,558 "	"	" "	"		86	7/8	13	
						MST	22 days	"	" "	"		33	0/8	65	
275568	Phenthyrine	Boiled starch	AKA-TOL	" " " " "	56	Tumor vol	3,873 mm³	"	2–6	60		47	6/6	7	
						" "	8,334 "	"	"	"		22	5/6	13	
						" "	17,149 "	"	"	"		28	"	20	
						MST	28 days	"	"	"		0	3/6	45	
			RShM-5	" " " " "	57	Tumor vol	273 mm³	"	"	"		67	7/7	7	
						" "	1,288 "	"	"	"		22	"	14	
				" " " " "	58	" "	4,371 "	"	"	"		15	"	21	
						MST	48.3 days	"	"	"		27	0/7	83	
			S37	sc, 10^6 cells	59	Tumor vol	429 mm³	"	2,6	200		60	7/7	7	
						" "	2,629 "	"	" "	"		78	"	12	
						" "	6,398 "	"	" "	"		71	"	26	
						" "	24,475 "	"	" "	"		53	"	33	
						MST	62.3 days	"	" "	"		10	1/7	109	
			S180	sc, 50 mg tumor susp	60	Tumor vol	954 mm³	"	2–6	60		40	6/6	7	
						" "	3,536 "	"	"	"		0	5/6	14	
						" "	11,676 "	"	"	"		+14	"	21	
			CaOv			[³H]dThd incl									1
			CaOv			NA content									7
			CaOv			Pro "									10
23909	Methyl-nitrosourea	Twice-distilled H_2O or saline	L1210	ip, 1.5×10^6 cells	241, 242	MST	8 days	ip	1	80		100	0/10		
						"	" "	"	1,6	67		62	"		
						"	" "	"	1–5	20		75	"		
			P388	ip, 10^6 cells	825	"	10.4 "	"	"	15–20	20	130	1/10	31	
			La	" " "	826	"	8 "	"	1,5	40–80	60	40	0/7	17	
			Ca-755	sc, 50 mg tumor susp	827	Tumor vol	122 mm³	"	2,6	30–70	70	71	7/7	7	
						" "	2,846 "	"	" "	"	"	87	6/7	11	
						" "	6,832 "	"	" "	"	"	76	"	14	
						" "	18,922 "	"	" "	"	"	86	5/7	18	
						MST	26.9 days	"	" "	"	"	12	0/7	47	
				" " " " "	249	Tumor wt	4.4 g	"	3–8	20	20	60	10/10	12	
						" "	" "	"	"	10		55	"	"	
						" "	" "	sc	"	50		65	"	"	
						" "	" "	"	"	20	"	60	"	"	
						Tumor vol	949 mm³	ip	2–6	"		78	8/8	7	
						" "	13,980 "	"	"	"		41	"	12	
						" "	29,064 "	"	"	"		40	6/8	17	
						MST	18.6 days	"	"	"		13	2/8	26	
			AKA-TOL	" " " " "	828	Tumor vol	1,456 mm³	"	"	15		83	6/6	8	
						" "	4,194 "	"	"	"		79	"	13	

			"	"	5,258 "	"	"	"		22	"	19
RShM-5	" " " " "	829	"	"	453 "	sc	2,6	30–70	50	61	8/8	7
			"	"	2,246 "	"	" "	"	"	32	"	13
			"	"	5,084 "	"	" "	"	"	16	"	19
			"	"	10,510 "	"	" "	"	"	54	7/8	25
			MST		42.9 days	"	" "	"	"	23	0/8	65
Ehrlich	ip, 6×10^6 cells	243	[b]		8.5 ml, 400×10^6	ip	1–6	20	20	90	10/10	8
			"	" "	"	"	"	10		80	"	"
			"	" "	"	"	"	6		50	"	"
			"	" "	"	sc	"	50		95	"	"
			"	" "	"	"	"	20	"	80	"	"
			"	" "	"	"	"	10		75	"	"
			"	" "	"	"	"	5		45	"	"
S180	" " "	244	"		4.4 ml, 380×10^6	ip	"	20	"	90	"	"
			"	" "	"	"	"	10		80	"	"
			"	" "	"	"	"	5		50	"	"
			"	" "	"	sc	"	50		85	"	"
			"	" "	"	"	"	20	"	75	"	"
			"	" "	"	"	"	10		30	"	"
S37	" " "	245	"		5.4 ml, 400×10^6	ip	"	20	"	90	"	"
			"	" "	"	"	"	10		70	"	"
			"	" "	"	"	"	5		50	"	"
			"	" "	"	sc	"	50	50	70	"	"
			"	" "	"	"	"	20		60	"	"
			"	" "	"	"	"	10		10	"	"
NK/Ly	" " "	246	"		5.0 ml, 800×10^6	ip	"	20	20	85	"	10
			"	" "	"	"	"	10		40	"	"
			"	" "	"	sc	"	20		70	"	"
			"	" "	"	"	"	50	50	90	"	"
LL	sc, 50 mg tumor susp	247, 248	Tumor wt		6.7 g	ip	7,13	67		60	"	24
			"	"	4.0 "	"	" "	20	20	70	"	18
			"	"	" "	"	" "	10		60	"	"
			"	"	" "	sc	7,12	50		75	"	"
			"	"	" "	"	" "	20	"	60	"	"
C3H mammary [c]	sc, 70 mg tumor susp	250	"	"	3.0 "	ip	12,14,16, 18,20,22	"		90	"	40
			"	"	" "	"	"	10	"	85	"	"
			"	"	" "	sc	"	50		90	"	"
			"	"	" "	"	"	20	"	85	"	"
			"	"	4.2 "	ip	21	100		75	"	48
Walker 256	" " " " "	251,	"	"	64.4 "	"	3,10	67		90	"	16
		252, 253	"	"	15 "	"	" "	20	"	95	"	10
			"	"	" "	"	" "	10		90	"	"
			"	"	" "	"	" "	5		80	"	"
			"	"	" "	sc	3–8	20	"	95	"	"
			"	"	" "	"	"	10		60	"	"
			"	"	" "	"	"	5		25	"	"
S45	" " " " "	254	"	"	26 "	ip	7–12	20	"	95	"	18
			"	"	" "	"	"	10		90	"	"
			"	"	" "	"	"	5		80	"	"

APPENDIX III.—*Results of experimental studies in the Soviet Union with drugs developed there* [a] *(Continued)*

NSC No.	Compound	Drug vehicle	Tumor	Site and inoculum	Expt. No.	Parameter of effect	Controls	Treatment: Route	Treatment: Schedule, days	Doses, mg/kg/injection: Tested	Doses, mg/kg/injection: Optimal	Percent ILS or tumor inhibition	Survivors/total	Day of evaluation	ED50, ug/ml
23909	Methyl-nitro-sourea	Twice-distilled H_2O or saline	S45	sc, 70 mg tumor susp	254	Tumor wt	26 g	sc	7–12	20	20	90	10/10	18	
						" "	" "	"	"	10		85	"	"	
						" "	" "	"	"	5		70	"	"	
			CaOv			[^{3}H]dThd incl									70
			CaOv			NA content									~200
			CaOv			Pro "									~300

[a] ED50 = median inhibitory concentration; MST = mean survival time; LL = Lewis lung; susp = suspension; NA = nucleic acid; [^{3}H]dThd incl = tritiated thymidine included; Pro = protein; it = intratesticular; q = every; fl = fluid; frag = fragment; Mel. H.P. = Harding Passey melanoma; prec = precipitate. Some data were not available.

[b] Parameter of effect for all of expt 243, 244, 245, and 246 with the Ehrlich, S180, S37, and NK/Ly tumors, respectively, were volume of ascites and total No. of tumor cells.

[c] Tumor was third generation and spontaneous.

APPENDIX IV.—*Results of experimental studies in the Soviet Union with drugs developed in the United States* [a]

NSC No.	Compound	Drug vehicle	Tumor	Site and inoculum	Expt. No.	Parameter of effect [b]	Controls	Treatment Route	Treatment Schedule, days	Doses, mg/kg/injection Tested	Doses, mg/kg/injection Optimal	Percent ILS or tumor inhibition	Survivors/total	Day of evaluation	ED50, μg/ml
26271	Cyclophosphamide	Saline	L1210	ip, 1×10^6	293	MST	8.5 days	ip	2, 6	25–400	100	117	2/3	69	
			La	ip, 7×10^6	294	"	7.3 "	"	0	100		129	0/10	27	
				" "		"	" "	"	1	"		105	"	"	
				" "		"	" "	"	5	"		93	0/11	"	
			MOPC 406	ip, 50 mg tumor susp	295, 296	"	14.7 "	"	2, 6	"	100	118	1/6	37	
				" " " " "		"	21.7 "	"	3	"		42	0/10	"	
				" " " " "		"	" "	"	7	"		113	0/7	100	
			LL	sc, " " " "	297	Tumor vol	1,518 mm^3	"	2–6	40		96	6/6	7	
				" " " " "		" "	11,514 "	"	"	"		83	"	13	
				" " " " "		" "	15,093 "	"	"	"		65	5/6	16	
				" " " " "		MST	19.7 days	"	"	"		46	0/6	56	
				" " " " "		Tumor vol	1,158 mm^3	"	2, 6	100		99	6/6	7	
				" " " " "		" "	11,514 "	"	" "	"		100	"	13	
				" " " " "		MST	19.7 days	"	" "	"		130	1/6	56	
				" " " " "	298	Tumor vol	465 mm^3	"	4, 18	200		52	10/10	6	
				" " " " "		" "	3,740 "	"	" "	"		99.6	"	11	
				" " " " "		" "	8,561 "	"	" "	"		96	"	15	
				" " " " "		" "	15,234 "	"	" "	"		86	"	20	
				" " " " "		" "	23,979 "	"	" "	"		90	"	26	
				" " " " "		MST	26.8 days	"	" "	"		90	0/10	56	
			Ca-755	" " " " "	299	Tumor vol	443 mm^3	"	2, 6	100	100	91	6/6	7	
				" " " " "		" "	5,549 "	"	" "	"	"	99	"	13	
				" " " " "		" "	11,007 "	"	" "	"	"	94	"	17	
				" " " " "		MST	22.3 days	"	" "	"	"	50	0/6	39	
			AKA-TOL	" " " " "	300	Tumor vol	257 mm^3	"	" "	75		97	14/14	7	
				" " " " "		" "	3,648 "	"	" "	"		99.9	"	13	
				" " " " "		" "	11,233 "	"	" "	"		99.9	"	19	
				" " " " "		MST	28.6 days	"	" "	"		130	1/14	105	
				" " " " "	301–303	Tumor vol	627 mm^3	"	" "	100		61	7/7	7	
				" " " " "		" "	1,698 "	"	" "	"		93	"	14	
				" " " " "		" "	3,638 "	"	" "	"		97	"	20	
				" " " " "		" "	6,638 "	"	" "	"		86	"	27	
				" " " " "		MST	44.2 days	"	" "	"		44	0/7	140	
			RShM-5	" " " " "	304	Tumor vol	112 mm^3	"	" "	"		96	7/7	7	
				" " " " "		" "	1,489 "	"	" "	"		99.9	"	14	
				" " " " "		" "	5,771 "	"	" "	"		99.4	"	22	
				" " " " "		" "	10,985 "	"	" "	"		96	"	29	
				" " " " "		MST	41.5 days	"	" "	"		72	2/7	85	
				" " " " "	305	Tumor vol	425 mm^3	"	7	200		74	9/9	10	
				" " " " "		" "	1,366 "	"	"	"		97	6/9	14	
				" " " " "		" "	4,051 "	"	"	"		98	5/9	20	
				" " " " "		" "	9,324 "	"	"	"		91	"	27	

				" " " " "			MST	41.4 days	"	"	"		2	0/9	77		
				" " " " "		304	Tumor vol	112 mm³	"	2–6	40		71	7/7	7		
				" " " " "			" "	1,489 "	"	"	"		70	"	14		
				" " " " "			" "	5,771 "	"	"	"		62	"	22		
				" " " " "			" "	10,985 "	"	"	"		27	"	29		
				" " " " "			MST	41.5 days	"	"	"		6	0/7	85		
			PRZh	im, " " " "		306	Tumor vol	6,148 mm³	"	2, 6	100	100	7	6/6	7		
				" " " " "			" "	11,231 "	"	" "	"	"	18	5/6	13		
				" " " " "			" "	14,399 "	"	" "	"	"	+34	4/6	18		
				" " " " "			MST	45.8 days	"	" "	"	"	33	0/6	67		
			S37	sc, 10^6 cells		307, 308	Tumor vol	348 mm³	"	" "	"	"	98	8/8	7		
				" " "			" "	1,308 "	"	" "	"	"	99.8	"	14		
				" " "			" "	2,232 "	"	" "	"	"	99.9	"	18		
			S180	sc, 50 mg tumor susp		309	" "	1,094 "	"	" "	"	"	97	6/6	7		
				" " " " "			" "	5,123 "	"	" "	"	"	99	"	14		
				" " " " "			" "	9,017 "	"	" "	"	"	92	"	21		
				" " " " "			MST	34 days	"	" "	"	"	44	4/6	56		
			S37	" " " " "			NA content									500	
			L5178Y	" " " " "			" "									"	
			Ehrlich	" " " " "			" "									"	
			NK/Ly	" " " " "			" "									"	
			CaOv	" " " " "			[³H]dThd incl									> 1,000	
			CaOv	" " " " "			NA content									> 100	
			CaOv	" " " " "			Pro "									> 1,000	
409962	1,3-Bis(2-chloroethyl)-1-nitrosourea	Saline	L1210	ip, 10^6 cells		325	MST	8.3 days	"	" "	20–35	35	700	0/6	90		
			La	" " "		803	"	8.0 "	"	1, 5	25–40	"	12	"	17		
			LL	sc, 50 mg tumor susp		326	Tumor vol	949 mm³	"	4, 11	40		43	10/10	7		
				" " " " "			"	4,288 "	"	" "	"		67	"	11		
				" " " " "			"	6,772 "	"	" "	"		59	9/10	15		
				" " " " "			"	13,340 "	"	" "	"		52	"	24		
				" " " " "			MST	27.5 days	"	" "	"		20	1/10	43		
			Ca-755	" " " " "		327	Tumor vol	604 mm³	"	2, 6	20–35	"	82	8/8	7		
				" " " " "			" "	6,642 "	"	" "	"	"	80	7/8	13		
				" " " " "			" "	14,448 "	"	" "	"	"	86	"	18		
			AKA-TOL	" " " " "		328	" "	487 "	"	5, 12	40		39	10/10	6		
				" " " " "			" "	1,068 "	"	" "	"		77	"	10		
				" " " " "			" "	6,756 "	"	" "	"		98	"	26		
				" " " " "			" "	8,889 "	"	" "	"		85	5/10	38		
				" " " " "			MST	56.6 days	"	" "	"		4	1/10	99		
				" " " " "		329	Tumor vol	210 mm³	"	2, 6	20–35	35	96	6/6	7		
				" " " " "			" "	4,100 "	"	" "	"	"	82	5/6	14		
				" " " " "			" "	12,807 "	"	" "	"	"	79	"	22		
				" " " " "			MST	32.7 days	"	" "	"	"	13	0/6	54		
			RShM-5	" " " " "		330	Tumor vol	425 mm³	"	7, 14	40		67	9/9	10		
				" " " " "			" "	1,366 "	"	" "	"		97	"	14		
				" " " " "			" "	4,051 "	"	" "	"		99.7	"	20		
				" " " " "			" "	9,824 "	"	" "	"		"	"	27		
				" " " " "			MST	41.4 days	"	" "	"		64	1/9	77		

APPENDIX IV.—*Results of experimental studies in the Soviet Union with drugs developed in the United States* [a] *(Continued)*

NSC No.	Compound	Drug vehicle	Tumor	Site and inoculum	Expt. No.	Parameter of effect [b]	Controls	Treatment: Route	Treatment: Schedule, days	Doses, mg/kg/injection: Tested	Doses, mg/kg/injection: Optimal	Percent ILS or tumor inhibition	Survivors/total	Day of evaluation	ED50. µg/ml
409962	1,3-Bis(2-chloroethyl)-1-nitrosourea	Saline	PRZh	im, 50 mg tumor susp	331, 332	Tumor vol	2 937 mm³	ip	2, 6	35		+96	8/8	7	
				" " " " "		" "	7,230 "	"	" "	"		81	"	13	
				" " " " "		" "	9,082 "	"	" "	"		9	"	20	
			S37	" " " " "		NA content									10–1
			L5178Y	" " " " "		" "									"
			Ehrlich	" " " " "		" "									"
			NK/Ly	" " " " "		" "									"
79037	1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea	Boiled starch	L1210	ip, 10^6 cells	333, 334	MST	8.3 days	Oral	" "	20–30	30	600	0/6	90	
				" " "		"	8.4 "	ip	2	40		419	3/8	141	
			La	" " "	335	"	7.8 "	"	"	"		10	0/7	8	
			MOPC 406	" 50 mg tumor susp	336, 337	"	14.7 "	Oral	2, 6	30		0	0/6	37	
				" " " " "		"	15.0 "	ip	3	40		"	0/8	23	
			LL	sc, " " " "	338	Tumor vol	491 mm³	Oral	2, 6	30		94	6/6	7	
				" " " " "		" "	2,987 "	"	" "	"		99.7	"	13	
				" " " " "		" "	17,231 "	"	" "	"		95	5/6	26	
				" " " " "		" wt	12.4 g	"	" "	"		88	4/6	36	
				" " " " "	339	" vol	204 mm³	"	4	50		39	11/11	5	
				" " " " "	340	" "	1,890 "	"	"	"		58	"	8	
				" " " " "		" "	6,053 "	"	"	"		16	10/11	13	
				" " " " "		MST	24.9 days	"	"	"		"	0/11	39	
			Ca-755	" " " " "	341, 342	Tumor vol	443 mm³	"	2, 6	20–30	30	48	6/6	7	
				" " " " "		" "	5,549 "	"	" "	"		39	"	13	
				" " " " "		" "	11,007 "	"	" "	"		53	5/6	17	
				" " " " "		MST	22.3 days	"	" "	"		38	0/6	39	
			AKA-TOL	" " " " "	343, 344	Tumor vol	1,776 mm³	"	" "	30		68	9/9	7	
				" " " " "		" "	4,184 "	"	" "	"		79	"	13	
				" " " " "		" "	14,002 "	"	" "	"		75	"	23	
				" " " " "		Tumor wt	13.8 g	"	" "	"		43	7/9	42	
			RShM-5	" " " " "	345	" vol	111 mm³	"	2–6	12		60	8/8	7	
				" " " " "		" "	1,124 "	"	"	"		63	"	14	
				" " " " "		" "	6,689 "	"	"	"		55	"	23	
				" " " " "		MST	39.1 days	"	"	"		5	0/8	62	
				" " " " "		Tumor vol	111 mm³	"	2, 6	30		70	8/8	7	
				" " " " "		" "	1,124 "	"	" "	"		68	"	14	
				" " " " "		" "	6,689 "	"	" "	"		34	"	23	
				" " " " "		MST	39.1 days	"	" "	"		9	1/8	62	
			PRZh	im, " " " "	346, 347	Tumor vol	6,148 mm³	"	" "	"		3	6/6	7	
				" " " " "		" "	11,231 "	"	" "	"		+43	"	13	
				" " " " "		MST	45.8 days	"	" "	"		31	0/6	67	
			S37	sc, 10^6 cells	348, 349	Tumor vol	348 mm³	"	" "	"		65	8/8	7	
				" " "		" "	1,308 "	"	" "	"		31	"	14	
				" " "		" "	3,168 "	"	" "	"		+19	"	23	
				" " "		MST	61.0 days	"	" "	"		19	0/8	91	

			S180	" 50 mg tumor susp	350	Tumor vol	1,094 mm³	"	" "	"		29	6/6	7			
				" " " " "		" "	5,123 "	"	" "	"		"	"	14			
				" " " " "		" "	9,017 "	"	" "	"		16	5/6	21			
				" " " " "		MST	34.0 days	"	" "	"		0	1/6	56			
34462	Uracil mustard	1% Ethyl alcohol	L1210	ip, 10^6 cells	287	"	8.3 "	ip	2–6	0.4–0.5	0.4	12	0/6	90			
				" " "	288	"	8.4 "	"	1–6	0.4–1.2	"	55	0/4	14			
				" " "	289	"	" "	"	1, 5	"	1.2	49	"	"			
			La	" " "	290	"	8.0 "	"	1–5	0.4		221	0/7	41			
				" " "		"	9.4 "	"	"	0.4–0.6	0.6	42	"	19			
			LL	sc, 50 mg tumor susp	291	Tumor vol	397 mm³	"	2–6	0.5		75	7/7	7			
				" " " " "		" "	6,628 "	"	"	"		36	"	10			
				" " " " "		" "	15,574 "	"	"	"		37	"	17			
				" " " " "		" "	19,271 "	"	"	"		33	6/7	27			
				" " " " "		MST	21.2 days	"	"	"		26	0/7	35			
			AKA-TOL	" " " " "	292	Tumor vol	154 mm³	"	"	0.4		99.6	9/9	7			
				" " " " "		" "	5,799 "	"	"	"		99.1	"	14			
				" " " " "		" "	9,875 "	"	"	"		76	0/9	19			
				" " " " "		" "	21,249 "	"	"	"		66	9/9	24			
				" " " " "		" "	22,745 "	"	"	"		40	"	31			
				" " " " "		MST	32.8 days	"	"	"		16	0/9	44			
			Ca-755	" " " " "	804	Tumor vol	122 mm³	"	"	0.4–0.8	0.8	45	7/7	7			
				" " " " "		" "	2,846 "	"	"	"	"	70	"	11			
				" " " " "		" "	6,832 "	"	"	"	"	48	"	14			
				" " " " "		" "	18,922 "	"	"	"	"	33	"	18			
				" " " " "		MST	26.9 days	"	"	"	"	0	0/7	47			
			RShM-5	" " " " "	805	Tumor vol	452 mm³	"	"	0.3–0.75	0.4	42	7/7	7			
				" " " " "		" "	2,738 "	"	"	"	"	59	"	13			
				" " " " "		" "	6,326 "	"	"	"	"	52	"	19			
				" " " " "		" "	12,761 "	"	"	"	"	42	"	25			
				" " " " "		MST	38.5 days	"	"	"	"	29	0/7	65			
			S37		6	NA content											20–10
			L5178Y	" " " " "		" "											50–20
			NK/Ly	" " " " "		" "											10
			Ehrlich	" " " " "		" "											"
82196	TIC-mustard	Saline	L1210	ip, 10^6 cells	310, 311	MST	7.1 "	"	2–7	100–200	150	120	0/6	18			
			La	" 5×10^6	312,313	"	8.8 "	"	1–5	60		28	"	63			
			MOPC 406	" 50 mg tumor susp	314	"	17 "	"	2, 6	120		7	0/8	93			
			LL	sc, " " " "	315	Tumor vol	2,693 mm³	"	2–6	60		27	7/7	7			
				" " " " "		" "	14,775 "	"	"	"		56	"	13			
				" " " " "		" "	18,001 "	"	"	"		12	5/7	20			
				" " " " "		MST	21.3 days	"	"	"		8	0/7	35			
				" " " " "		Tumor vol	2.693 mm³	"	2, 6	120		49	7/7	7			
				" " " " "		" "	14,775 "	"	"	"		46	"	13			
				" " " " "		" "	18,001 "	"	"	"		+2	"	20			
				" " " " "		MST	21.3 days	"	"	"		30	0/7	35			

APPENDIX IV.—*Results of experimental studies in the Soviet Union with drugs developed in the United States* [a] *(Continued)*

NSC No.	Compound	Drug vehicle	Tumor	Site and inoculum	Expt. No.	Parameter of effect [b]	Controls	Treatment: Route	Treatment: Schedule, days	Doses, mg/kg/injection: Tested	Doses, mg/kg/injection: Optimal	Percent ILS or tumor inhibition	Survivors/total	Day of evaluation	ED50, μg/ml
82196	TIC-mustard	Saline	Ca-755	sc, 50 mg tumor susp	316, 317	Tumor vol	9,220 mm³	ip	2–6	60		70	6/6	7	
				" " " " "		" "	17,996 "	"	"	"		14	"	14	
				" " " " "		MST	22.3 days	"	"	"		1	0/6	33	
			Ca-755	" " " " "	318, 319	Tumor wt	6.5 g	"	3–7	100–200		35	5/6	16	
			AKA-TOL	" " " " "	320	" vol	319 mm³	"	2, 6	120		+97	7/7	7	
				" " " " "		" "	563 "	"	" "	"		18	"	13	
				" " " " "		" "	4,056 "	"	" "	"		3	"	24	
				" " " " "		MST	82.6 days	"	" "	"		22	0/7	108	
			RShM-5	" " " " "	321	Tumor vol	95 mm³	"	" "	"		36	7/7	7	
				" " " " "		" "	2,157 "	"	" "	"		25	"	13	
				" " " " "		" "	4,662 "	"	" "	"		23	"	20	
				" " " " "		" "	11,221 "	"	" "	"		10	5/7	30	
				" " " " "		MST	54.8 days	"	" "	"		0	0/7	79	
			RShM-5	" " " " "		Tumor vol	95 mm³	"	2–6	60		7	7/7	7	
				" " " " "		" "	2,157 "	"	"	"		61	"	13	
				" " " " "		" "	11,221 "	"	"	"		52	"	30	
				" " " " "		MST	54.8 days	"	"	"		11	1/7	79	
			PRZh	im, " " " "	322	Tumor vol	8,818 mm³	"	"	"		+2	8/8	7	
				" " " " "		" "	16,120 "	"	"	"		2	"	13	
				" " " " "		" "	31,008 "	"	"	"		+10	5/8	27	
				" " " " "		MST	41.1 days	"	"	"		14	1/8	82	
			S37	sc, 10^6 cells	323, 324	Tumor vol	348 mm³	"	2, 6	120		79	8/8	7	
				" " "		" "	1,308 "	"	"	"		42	"	14	
				" " "		" "	2,232 "	"	"	"		57	"	10	
				" " "		" "	3,168 "	"	"	"		43	"	23	
				" " "		MST	61 days	"	"	"		0	0/8	91	
			S37	" " " " "		NA content									50–20
			L5178Y	" " " " "		" "									100–50
			Ehrlich	" " " " "		" "									"
			NK/Ly	" " " " "		" "									"
85998	Streptozotocin	Saline	L1210	ip, 10^5 cells	753	MST	8.2 "	"	2–6	50		28	0/6	14	
			P388	" 10^6 "	754	"	10.4 "	"	1–5	"		63	0/10	20	
			La	ip, 3.5×10^6 cells	755	"	7.1 "	"	"	"		107	0/6	46	
				" " "	757	"	8.6 "	"	1–6	"		24	0/8	17	
			MOPC	" 50 mg tumor susp	758	"	15.1 "	"	2–8	40		63	0/7	38	
			406	" " " " "	759	"	12.5 "	"	3–10	50–60	50	33	0/8	17	
			LL	sc, " " " "	760	Tumor vol	2,693 mm³	"	2–6	50		+8	7/7	7	
				" " " " "		" "	14,755 "	"	"	"		43	"	13	
				" " " " "		MST	21.3 days	"	"	"		0	0/7	35	
			Ca-755	" " " " "	761, 762	Tumor vol	403 mm³	"	"	"		45	8/8	7	
				" " " " "		" "	8,358 "	"	"	"		+20	"	13	
				" " " " "		MST	22.0 days	"	"	"		7	0/8	65	

			AKA-TOL	"	"	"	"	"	763–765	Tumor vol	466 mm³	"	"	40–50	50	51	8/8	7
				"	"	"	"	"		" "	1,930 "	"	"	"	"	80	"	13
				"	"	"	"	"		" "	4,139 "	"	"	"	"	68	"	20
				"	"	"	"	"		" "	11,013 "	"	"	"	"	41	"	34
				"	"	"	"	"		MST	52.0 days	"	"	"	"	27	0/8	104
			RShM-5	"	"	"	"	"	766, 767	Tumor vol	273 mm³	"	"	"	40	55	7/7	7
				"	"	"	"	"		" "	1,288 "	"	"	"	"	+3	"	14
				"	"	"	"	"		" "	4,371 "	"	"	"	"	+12	"	21
				"	"	"	"	"		MST	48.3 days	"	"	"	"	14	0/7	83
			PRZh	im,	"	"	"	"	768	Tumor vol	3.459 mm³	"	"	50		30	8/8	7
				"	"	"	"	"		" "	5,904 "	"	"	"		22	"	13
				"	"	"	"	"		MST	42 days	"	"	"		"	0/8	97
			S37	sc, 10^6 cells					769–771	Tumor vol	429 mm³	"	"	40–50		34		7
				"	"	"				" "	2,629 "	"	"	"		15		12
			S180	"	50 mg tumor susp				772, 773	" "	1,487 "	"	"	40		45	6/6	7
				"	"	"	"	"		" "	5,647 "	"	"	"		+18	"	14
				"	"	"	"	"		" "	11,093 "	"	"	"		+64	"	21
13875	Hexa-methyl-melamine	Boiled starch	L1210	ip, 10^6 cells					360	MST	7.6 days	Oral	"	70		13	0/6	13
			La	"	5×10^6				361	"	13.8 "	"	"	125		48	"	69
			MOPC 406	"	50 mg tumor susp				362	"	15.1 "	"	"	"		16	0/7	38
			LL	sc,	"	"	"	"	363	Tumor vol	2,040 mm³	"	"	"		38	6/6	7
				"	"	"	"	"		" "	7,359 "	"	"	"		39	"	13
				"	"	"	"	"		MST	22.1 days	"	"	"		18	0/6	34
			Ca-755	"	"	"	"	"	364, 365	Tumor vol	288 mm³	"	"	75–200	125	30	9/9	6
				"	"	"	"	"		" "	1,670 "	"	"	"	"	75	"	10
				"	"	"	"	"		" "	4,801 "	"	"	"	"	73	"	13
				"	"	"	"	"		" "	11,972 "	"	"	"	"	69	"	17
				"	"	"	"	"		MST	24.2 days	"	"	"	"	22	0/9	41
			AKA-TOL	"	"	"	"	"	366	Tumor vol	1,371 mm³	"	"	125		52	7/7	7
				"	"	"	"	"		" "	5,331 "	"	"	"		48	"	13
				"	"	"	"	"		" "	9,986 "	"	"	"		43	"	20
				"	"	"	"	"		MST	69.6 days	"	"	"		25	0/7	80
			RShM-5	"	"	"	"	"	367, 368	" "	273 mm³	"	"	75–200	"	87	7/7	7
				"	"	"	"	"		" "	1,288 "	"	"	"	"	76	"	14
				"	"	"	"	"		" "	4,371 "	"	"	"	"	63	"	21
				"	"	"	"	"		" "	8,231 "	"	"	"	"	30	"	28
				"	"	"	"	"		MST	48.3 days	"	"	"	"	19	0/7	83
			PRZh	"	"	"	"	"	369	Tumor vol	2,937 mm³	"	"	125		12	8/8	7
				"	"	"	"	"		" "	7,230 "	"	"	"		31	"	13
				"	"	"	"	"		" "	9,082 "	"	"	"		12	"	20
				"	"	"	"	"		Tumor wt	8.8 g	"	"	"		+19	"	28
			S37	"	10^6 cells				370, 371	" vol	519 mm³	"	"	75–125	"	52	6/6	7
				"	"	"				" "	2,629 "	"	"	"	"	93	"	12
				"	"	"				" "	6.398 "	"	"	"	"	65	"	19
				"	"	"				" "	11,295 "	"	"	"	"	61	5/6	26
				"	"	"				MST	62.3 days	"	"	"	"	32		52
			S180	"	50 mg tumor cells				372	Tumor vol	1,487 mm³	"	"	125		37	6/6	7
				"	"	"	"	"		" "	5,647 "	"	"	"		24	"	14
				"	"	"	"	"		" "	11,093 "	"	"	"		34	"	21

APPENDIX IV.—*Results of experimental studies in the Soviet Union with drugs developed in the United States* [a] *(Continued)*

NSC No.	Compound	Drug vehicle	Tumor	Site and inoculum	Expt. No.	Parameter of effect [b]	Controls	Treatment Route	Treatment Schedule, days	Doses, mg/kg/injection Tested	Doses, mg/kg/injection Optimal	Percent ILS or tumor inhibition	Survivors/total	Day of evaluation	ED50, ug/ml
19893	5-Fluorouracil	Saline	L1210	ip, 10^6 cells	476–481	MST	8.7 days	ip	2–8	10–30	25	75	0/6	31	
				" " "		"	" "	"	2–11	10–20	20	84	"	"	
				" " "		"	" "	"	2, 6	50	50	94	0/5	16	
			La	" 5×10^6 cells	482, 483	"	8.3 "	"	" "	"		339	2/7	63	
			MOPC 406	" 50 mg tumor susp	484, 485	"	15.1 "	"	" "	50–65	"	110	1/6	38	
			LL	sc, " " " "	486–488	Tumor vol	2,693 mm^3	"	2–6	25		93	7/7	7	
				" " " " "		" "	14,775 "	"	"	"		63	6/7	13	
				" " " " "		" "	18,001 "	"	"	"		7	5/7	20	
				" " " " "		MST	21.3 days	"	"	"		0	0/7	35	
				" " " " "		Tumor vol	2,693 mm^3	"	2, 6	65		90	7/7	7	
				" " " " "		" "	14,775 "	"	" "	"		70	"	13	
				" " " " "		" "	18,001 "	"	" "	"		23	6/7	20	
				" " " " "		MST	21.3 days	"	" "	"		11	0/7	35	
			Ca-755	" " " " "	489–493	Tumor vol	822 mm^3	"	2–6	20		52	7/7	7	
				" " " " "		" "	18,380 "	"	"	"		29	"	15	
				" " " " "		" "	25,125 "	"	"	"		23	6/7	19	
				" " " " "		MST	24.1 days	"	"	"		9	0/7	35	
				" " " " "		Tumor vol	822 mm^3	"	2, 4, 6	30		58	7/7	7	
				" " " " "		" "	18,380 "	"	" " "	"		53	"	15	
				" " " " "		" "	25,125 "	"	" " "	"		46	6/7	19	
				" " " " "		MST	24.1 days	"	" " "	"		0	0/7	35	
				" " " " "		Tumor vol	822 mm^3	"	2, 5	50–65	65	92	7/7	7	
				" " " " "		" "	18,280 "	"	" "	"	"	60	"	15	
				" " " " "		" "	25,125 "	"	" "	"	"	52	"	19	
				" " " " "		MST	24.1 days	"	" "	"	"	13	0/7	35	
				" " " " "	806	Tumor vol	822 mm^3	"	2, 6	"	50	91	7/7	7	
				" " " " "		" "	18,380 "	"	" "	"	"	69	"	15	
				" " " " "		" "	25,125 "	"	" "	"	"	54	"	19	
				" " " " "		MST	24.1 days	"	" "	"	"	19	0/7	35	
			AKA-TOL	" " " " "	494–496	Tumor vol	487 mm^3	"	" "	20		6	10/10	6	
				" " " " "		" "	1,068 "	"	" "	"		43	"	10	
				" " " " "		" "	6,756 "	"	" "	"		11	9/10	26	
				" " " " "		MST	56.6 days	"	" "	"		22	0/10	99	
			RShM-5	" " " " "	497, 498	Tumor vol	184 mm^3	"	" "	65		37	6/6	9	
				" " " " "		" "	1,308 "	"	" "	"		32	5/6	13	
				" " " " "		" "	3,644 "	"	" "	"		46	"	17	
				" " " " "		MST	41.4 days	"	" "	"		0	0/6	57	
			PRZh	im, " " " "	499	Tumor vol	3,459 mm^3	"	" "	50		27	8/8	7	
				" " " " "		" "	5,654 "	"	" "	"		26	"	13	
				" " " " "		MST	43 days	"	" "	"		6	0/8	97	
			S37	sc, 10^6 cells	500, 501	Tumor vol	336 mm^3	"	" "	65		73	7/7	7	
				" " "		" "	1,986 "	"	" "	"		22	"	13	
				" " "		" "	8,049 "	"	" "	"		+31	"	25	

				" " "			MST	52.7 days	"	" "	"		4	0/7	133	
			S180	" 50 mg tumor susp		502	Tumor vol	1,094 mm³	"	" "	50		18	6/6	7	
				" " " " "			" "	5,123 "	"	" "	"		+1	"	14	
				" " " " "			MST	34.0 days	"	" "	"		7	1/6	56	
			S37				NA content									< 0.1
			L5178Y				" "									"
			Ehrlich				" "									"
			NK/Ly				" "									< 1
			CaOv				[³H]dThd incl									> 1,000
			CaOv				NA content									20
			CaOv				Pro "									30
145663	Cyclocytidine	Saline	L1210	ip, 10^6 cells		503, 504	MST	7.0 "	"	1–5	100		99	0/7	15	
				" " "		505	"	7.4 "	"	1–8	"		127	0/8	18	
			P388	" " "		506	"	10.5 "	"	"	"		100	"	22	
			La	" 5×10^6 cells		507–509	"	8.8 "	"	1–6	100–120	120	28	0/7	63	
			MOPC 406	" 50 mg tumor susp		510	"	14.0 "	"	3, 7	400		0	0/6	18	
			LL	sc, " " " "		511, 512	Tumor vol	2,693 mm³	"	2–6	120		50	6/7	7	
				" " " " "			" "	14,775 "	"	"	"		35	3/7	13	
				" " " " "			MST	21.3 days	"	2, 6	"		3	0/7	35	
				" " " " "			Tumor vol	2,693 mm³	"	" "	400		40	7/7	7	
				" " " " "			" "	14,775 "	"	" "	"		29	6/7	13	
				" " " " "			MST	21.3 days	"	" "	"		0	0/7	35	
			Ca-775	" " " " "		513	Tumor vol	981 mm³	"	2–6	100		87	8/8	8	
				" " " " "			" "	10,226 "	"	"	"		51	"	13	
				" " " " "			" "	13,138 "	"	"	"		35	"	18	
				" " " " "		514, 515	" "	443 "	"	"	120		53	6/6	7	
				" " " " "			" "	5,549 "	"	"	"		+10	"	13	
				" " " " "			MST	22.3 days	"	"	"		19	0/6	39	
				" " " " "			Tumor vol	443 mm³	"	2, 6	400		+16	6/6	7	
				" " " " "			" "	5,549 "	"	" "	"		38	"	13	
				" " " " "			MST	24.1 days	"	" "	"		0	0/6	39	
			AKA-TOL	" " " " "		516	Tumor vol	319 mm³	"	" "	"		28	7/7	7	
				" " " " "			" "	563 "	"	" "	"		64	"	13	
				" " " " "			" "	4,056 "	"	" "	"		59	"	24	
				" " " " "			" "	6,776 "	"	" "	"		58	"	31	
				" " " " "			MST	82.6 days	"	" "	"		29	0/7	108	
			RShM-5	" " " " "		517	Tumor vol	270 mm³	"	2–6	120		30	7/7	7	
				" " " " "			" "	1,429 "	"	"	"		51	"	13	
				" " " " "			" "	3,863 "	"	"	"		30	"	20	
				" " " " "			MST	39.6 days	"	"	"		27	1/7	68	
				" " " " "		518	Tumor vol	270 mm³	"	2, 6	400		24	7/7	7	
				" " " " "			" "	1,429 "	"	" "	"		20	"	13	
				" " " " "			" "	3,863 "	"	" "	"		22	"	20	
				" " " " "			MST	39.6 days	"	" "	"		3	0/7	68	
			S37	" 10^6 cells		519, 520	Tumor vol	348 mm³	"	2–6	120		64	8/8	7	
				" " "			" "	1,308 "	"	"	"		40	"	14	
				" " "			" "	3,168 "	"	"	"		+48	"	23	
				" " "			MST	61.0 days	"	"	"		5	1/8	91	

APPENDIX IV.—*Results of experimental studies in the Soviet Union with drugs developed in the United States* [a] *(Continued)*

NSC No.	Compound	Drug vehicle	Tumor	Site and inoculum	Expt. No.	Parameter of effect [b]	Controls	Treatment: Route	Treatment: Schedule, days	Doses, mg/kg/injection: Tested	Doses, mg/kg/injection: Optimal	Percent ILS or tumor inhibition	Survivors/total	Day of evaluation	ED50, ug/ml
145663	Cyclocytidine	Ca-755	S37			NA content									20
			L5178Y			" "									500–250
			Ehrlich			" "									500
			NK/Ly			" "									"
102816	5-Azacytidine	Saline	L1210	ip, 10^6 cells	521–523	MST	8.0 days	ip	2–6	1–6	6	182	2/8	25	
				" " "		"	8.9 "	"	1–9	3		136	0/6	"	
			La	" 5×10^6 cells	524, 525	"	8.8 "	"	1–5	2–2.5	2.5	93	1/8	63	
			MOPC 406	" 50 mg tumor susp	526, 527	"	14.7 "	"	2–6	5		63	0/6	37	
				" " " " "		"	16.8 "	"	3–11	4		72	0/7	32	
			LL	sc, " " " "	528, 529	Tumor vol	1,266 mm^3	"	2–6	2		54	7/7	7	
				" " " " "		" "	4,831 "	"	"	"		+ 6	"	13	
				" " " " "		" "	16,805 "	"	"	"		13	"	22	
				" " " " "		" "	1,226 "	"	2, 6	5–8	8	72	"	7	
				" " " " "		" "	4,831 "	"	" "	"	"	39	"	13	
				" " " " "		" "	16,805 "	"	" "	"	"	36	"	22	
			Ca-755	" " " " "	530–532	" "	445 "	"	2–6	5–7	5	91	6/6	7	
				" " " " "		" "	5,549 "	"	"	"	"	96	"	13	
				" " " " "		" "	11,007 "	"	"	"	"	86	"	17	
				" " " " "		MST	23.3 days	"	"	"	"	42	0/6	39	
			AKA-TOL	" " " " "	533	Tumor vol	319 mm^3	"	"	2.5		52	7/7	7	
				" " " " "		" "	563 "	"	"	"		76	"	18	
				" " " " "		" "	1,394 "	"	"	"		91	"	24	
				" " " " "		" "	4,056 "	"	"	"		81	"	29	
				" " " " "		" "	10,763 "	"	"	"		39	"	39	
				" " " " "		MST	82.6 days	"	"	"		4	0/7	108	
			RShM-5	" " " " "	534	Tumor vol	144 mm^3	"	"	"		48	8/8	7	
				" " " " "		" "	1,116 "	"	"	"		13	"	13	
				" " " " "		" "	5,298 "	"	"	"		26	"	21	
				" " " " "		MST	40.2 days	"	"	"		2	1/8	59	
			PRZh	im, " " " "	535	Tumor vol	8,818 mm^3	"	"	"		14	8/8	7	
				" " " " "		" "	16,120 "	"	"	"		+ 3	"	13	
				" " " " "		" "	28,087 "	"	"	"		10	"	20	
				" " " " "		MST	41.1 days	"	"	"		18	0/8	82	
			S37	sc, 10^6 cells	536	Tumor vol	429 mm^3	"	"	"		+ 31	7/7	7	
				" " "		" "	2,629 "	"	"	"		+ 3	"	12	
				" " "		" "	6,398 "	"	"	"		40	"	19	
				" " "		" "	11,296 "	"	"	"		61	"	26	
				" " "		" "	24,474 "	"	"	"		33	"	33	
			S180	" 50 mg tumor susp	537	" "	1,081 "	"	2, 6	7.5		+ 60	10/10	7	
				" " " " "		" "	4,891 "	"	" "	"		+ 19	"	13	
				" " " " "		MST	30 days	"	" "	"		2	1/10	56	

			S37				NA content									0.1
			L5178Y				" "									10–1
			Ehrlich				" "									1
			NK/Ly				" "									10–1
119875	*cis*-Platinum (II) diamminedichloride	Saline	L1210	ip, 10^6 cells	385–387	MST	8.0	"	"	2–6	0.5–5	2.5	68	0/8	25	
				" " "	388, 389	"	"	"	"	1–5	2–4	4	142	2/6	100	
			La	" " "	390	"	7.8	"	"	1	8		200	0/6	26	
			MOPC 406	" 50 mg tumor susp	391	"	15.1	"	"	2–6	2		11	0/5	38	
			LL	sc, " " " "	392, 393	Tumor vol	204	mm^3	"	4	6		34	11/11	5	
				" " " " "		" "	1,890	"	"	"	"		61	8/11	8	
				" " " " "		" "	6,053	"	"	"	"		23	6/11	13	
				" " " " "		MST	24.9	days	"	"	"		18	0/11	39	
			Ca-755	" " " " "	394	Tumor vol	80	mm^3	"	3	8		90	7/7	7	
				" " " " "		" "	756	"	"	"	"		95	"	10	
				" " " " "		" "	7,203	"	"	"	"		88	"	18	
				" " " " "	395	" "	700	"	"	3–7	1.5–2.5	2.5	94	6/6	7	
				" " " " "		" "	8,558	"	"	"	"	"	78	"	16	
				" " " " "		" wt	11.2	g	"	"	"	"	60	"	18	
				" " " " "	396, 397	Tumor vol	568	mm^3	"	2–6	1.5		92	7/8	7	
				" " " " "		" "	8,769	"	"	"	"		85	"	13	
				" " " " "		" "	25,060	"	"	"	"		71	4/8	18	
				" " " " "		MST	24.7	days	"	"	"		0	0/8	48	
			AKA-TOL	" " " " "	398, 399	Tumor vol	665	mm^3	"	3–7	1.5–2.5	"	81	6/6	7	
				" " " " "		" "	1,901	"	"	"	"	"	91	"	14	
				" " " " "		" wt	3.4	g	"	"	"	"	85	"	16	
				" " " " "	400	" vol	664	mm^3	"	2–6	"	"	51	"	7	
				" " " " "		" "	1,901	"	"	"	"	"	91	"	13	
				" " " " "		" wt	2.8	g	"	"	"	"	89	"	16	
			RShM-5	" " " " "	401	" vol	531	mm^3	"	"	1–2		+ 5	7/7	7	
				" " " " "		" "	2,045	"	"	"	"		12	4/7	13	
				" " " " "		" "	4,908	"	"	"	"		+ 14	3/7	20	
			S37	" 10^6 cells	402	" "	455	"	"	4, 11	4		45	6/6	7	
				" " "		" "	4,233	"	"	" "	"		70	"	18	
				" " "		" "	12,833	"	"	" "	"		61	"	26	
				" " "		" "	455	"	"	4–8	2.5		25	"	7	
				" " "		" "	4,233	"	"	"	"		93	"	18	
				" " "		" "	12,833	"	"	"	"		80	"	26	
			S180	" 50 mg tumor susp	403	" "	2.089	"	"	"	3		76	"	10	
				" " " " "		" "	9,013	"	"	"	"		82	"	17	
				" " " " "		" "	17,001	"	"	"	"		70	"	23	
				" " " " "		" "	2 089	"	"	4, 7, 10, 13	5		73	"	10	
				" " " " "		" "	9,013	"	"	" " " "	"		83	5/6	17	
				" " " " "		" "	17,001	"	"	" " " "	"		80	"	23	
			S37				NA content									50
			L5178Y				" "									10
			Ehrlich				" "									"
			NK/Ly				" "									20–10

APPENDIX IV.—*Results of experimental studies in the Soviet Union with drugs developed in the United States* [a] *(Continued)*

NSC No.	Compound	Drug vehicle	Tumor	Site and inoculum	Expt. No.	Parameter of effect [b]	Controls	Treatment Route	Treatment Schedule, days	Doses, mg/kg/injection Tested	Doses, mg/kg/injection Optimal	Percent ILS or tumor inhibition	Survivors/total	Day of evaluation	ED50, μg/ml
119875	*cis*-Platinum (II) diamminedichloride	Saline	CaOv			[^{3}H]dThd incl									10
			CaOv			NA content									30
			CaOv			Pro "									50
15200	Gallium nitrate	Saline	L1210	ip, 10^6 cells	373, 374	MST	7.1 days	ip	2–6	60–75	60	8	0/6	8	
			La	" " "	375, 376	"	" "	"	"	45	245	245	"	46	
			MOPC 406	" 50 mg tumor susp	377	"	17.0 "	"	"	50		17	0/7	91	
			Ca-755	sc, " " " "	378, 379	Tumor wt	2.7 g	"	3–7	60–70	60	88	6/6	16	
				" " " " "		" vol	785 mm^3	"	2–6	35–55	45	92	9/10	7	
				" " " " "		" "	10,836 "	"	"	"	"	89	"	13	
				" " " " "		" "	20,580 "	"	"	"	"	71	"	18	
				" " " " "		" "	23,873 "	"	"	"	"	+4	"	25	
				" " " " "		MST	34.6 days	"	"	"	"	25	0/10	51	
			AKA-TOL	" " " " "	380	Tumor vol	1,371 mm^3	"	"	45		76	6/6	7	
				" " " " "		" "	5,331 "	"	"	"		"	"	13	
				" " " " "		" "	9,986 "	"	"	"		43	"	20	
				" " " " "		" "	12,068 "	"	"	"		21	"	26	
				" " " " "		MST	69.6 days	"	"	"		35	1/6	80	
			RShM-5	" " " " "	381	Tumor vol	112 mm^3	"	"	50		40	7/7	7	
				" " " " "		" "	1,489 "	"	"	"		+9	"	14	
				" " " " "		" "	5,771 "	"	"	"		0	"	22	
				" " " " "		MST	41.5 days	"	"	"		16	0/7	85	
				" " " " "		Tumor vol	112 mm^3	"	2, 6	60		36	7/7	7	
				" " " " "		" "	1,489 "	"	" "	"		0	"	14	
				" " " " "		MST	41.5 days	"	" "	"		20	0/7	85	
			S37	" 10^6 cells	382, 383	Tumor vol	348 mm^3	"	2–6	45–50	50	70	8/8	7	
				" " "		" "	1,308 "	"	"	"	"	0	7/8	14	
				" " "		" "	2,232 "	"	"	"	"	+31	"	18	
				" " "		MST	61 days	"	"	"	"	30	0/8	91	
			S180	" 50 mg tumor susp	384	Tumor vol	1,487 mm^3	"	"	45		46	6/6	7	
				" " " " "		" "	5,647 "	"	"	"		+22	3/6	14	
				" " " " "		MST	29.3 days	"	"	"		30	0/6	56	
			S37			NA content									100–50
			L5178Y			" "									100
			Ehrlich			" "									250–100
			NK/Ly			" "									100–50
1895	Guanazole	Saline	L1210	ip, 10^6 cells	538	MST	8.9 "	"	1–9	1,800		61	0/7	17	
			La	" 5×10^6	539, 540	"	13.8 "	"	Twice/day, 1–5	500		288	2/5	69	
			MOPC 406	" 50 mg tumor susp	541	"	15.0 "	"	3–8	2 000		49	0/8	29	

			LL	sc, " " " " "	542	Tumor vol	1,624 mm³	"	Twice/day, 2–6	500	47	8/8	7		
				" " " " "		" "	10,870 "	"	" " " "	"	25	"	13		
				" " " " "		MST	24 days	"	" " " "	"	4	0/8	41		
			Ca-755	" " " " "	543	Tumor vol	568 mm³	"	2–6	"	95	8/8	7		
				" " " " "		" "	8,769 "	"	"	"	71	"	13		
				" " " " "		" "	24,164 "	"	"	"	34	7/8	21		
				" " " " "		MST	24.7 days	"	"	"	18	0/8	48		
				" " " " "	544	Tumor wt	5.8 g	"	2, 4, 6	2,000	55	7/7	15		
			AKA-TOL	" " " " "	545	" vol	627 mm³	"	Thrice/day, 2–6	600	72	6/6	7		
				" " " " "		" "	1,698 "	"	" " " "	"	83	"	14		
				" " " " "		" "	3,638 "	"	" " " "	"	44	"	20		
				" " " " "		MST	44.2 days	"	" " " "	"	24	0/6	140		
				" " " " "		Tumor vol	627 mm³	"	" " "	1,300	46	7/7	7		
				" " " " "		" "	1,698 "	"	" " "	"	53	"	14		
				" " " " "		" "	3,638 "	"	" " "	"	15	"	20		
				" " " " "		MST	44.2 days	"	" " "	"	34	0/7	140		
			RShM-5	" " " " "	546	Tumor vol	144 mm³	"	Twice/day, 2–6	500	91	8/8	7		
				" " " " "		" "	1,116 "	"	" " " "	"	43	"	13		
				" " " " "		" "	5,298 "	"	" " " "	"	45	"	21		
				" " " " "		MST	40.2 days	"	" " "	"	24	2/8	59		
			PRZh	im, " " " "	547	"	41.1 "	"	2–6	1,000	8	0/8	82		
				" " " " "		Tumor vol	8,818 mm³	"	"	"	26	8/8	7		
				" " " " "		" "	16,120 "	"	"	"	+ 3	7/8	13		
				" " " " "		" "	28,087 "	"	"	"	16	"	20		
		Saline	S37	sc, 10^6 cells	548	" "	336 "	"	"	1,800	66	7/7	7		
				" " "		" "	1,986 "	"	"	"	6	"	13		
				" " "		" "	8,049 "	"	"	"	31	5/7	25		
				" " "		MST	52.7 days	"	"	"	22	0/7	133		
			S180	" 50 mg tumor susp	549	Tumor vol	1,081 mm³	"	Twice/day, 2–6	500	+ 60	9/9	7		
				" " " " "		" "	4,891 "	"	" " " "	"	18	7/9	13		
				" " " " "		MST	30 days	"	" " " "	"	1	0/9	56		
			S37			NA content									2,000
			L5178Y			" "									2,500
			Ehrlich			" "									250–100
			NK/Ly			" "									5,000–2,000
71795	Ellipticine	Boiled starch	P388	ip, 10^6 cells	774	MST	9.6 "	"	1, 4, 7	30	60	0/6	20		
			LL	sc, 50 mg tumor susp	775, 776	Tumor vol	1,980 mm³	"	3, 6, 9	50	0	7/7	8		
				" " " " "		" "	9,671 "	"	" " "	"	+ 10	6/7	12		
				" " " " "		" "	1,980 "	"	" " "	100	27	7/7	8		
				" " " " "		" "	9,671 "	"	" " "	"	18	6/7	12		
			RShM-5	" " " " "	777	" "	7,738 "	"	3, 6, 9, 12, 15	20	17	6/6	24		
			AKA-TOL	" " " " "	778	" "	539 "	"	3, 6, 9	30	13	"	10		
				" " " " "		" "	1,411 "	"	" " "	"	12	"	17		

APPENDIX IV.—*Results of experimental studies in the Soviet Union with drugs developed in the United States* [a] *(Continued)*

NSC No.	Compound	Drug vehicle	Tumor	Site and inoculum	Expt. No.	Parameter of effect [b]	Controls	Treatment: Route	Treatment: Schedule, days	Doses, mg/kg/injection: Tested	Doses, mg/kg/injection: Optimal	Percent ILS or tumor inhibition	Survivors/total	Day of evaluation	ED50, μg/ml
83265	*S*-Trityl-L-cysteine	Saline	L1210	ip, 10^6 cells	612, 614	MST	7.1 days	ip	2–6	100–200		6	0/6	8	
				" " " " "		"	" "	Oral	"	200–250	200	37	"	12	
			Ca-755	sc, 50 mg tumor susp	615, 616	Tumor wt	6.5 g	ip	3–7	80–250	"	52	3/6	16	
			S37			NA content									50
			L5178Y			" "									250–100
			Ehrlich			" "									500–250
			NK/Ly			" "									500
118994	Inosine diglycolaldehyde	Saline	L1210	ip, 10^6 cells	567	MST	7.6 days	"	1–5	100		32	0/6	10	
			P388	" " " " "	568	"	11.2 "	"	2, 6, 10	200		104	0/5	25	
			La	" " " " "	569	"	8.7 "	"	1–6	120		12	0/7	12	
				" " " " "	570–572	"	13.8 "	"	1, 5	200		193	2/6	69	
			MOPC	" 50 mg tumor susp	573	"	16.8 "	"	3–11	100–200	100	25	0/7	31	
			406	" " " " "		"	" "	"	3, 7, 11	"	200	27	"	"	
			LL	sc, " " " "	574–576	Tumor vol	2,397 mm^3	"	2, 6	200		18	7/7	7	
				" " " " "		" "	7,162 "	"	" "	"		+14	"	13	
				" " " " "		" "	18,665 "	"	" "	"		+5	"	24	
				" " " " "		MST	33.0 days	"	" "	"		5	0/7	50	
				" " " " "	577	Tumor wt	5.5 g	"	" "	"		22	7/7	13	
			Ca-755	" " " " "	578, 579	" "	2.3 "	"	2–6	100		4	5/5	15	
				" " " " "		" "	7.7 "	"	2, 6	200		27	6/6	16	
				" " " " "	580	" vol	568 mm^3	"	" "	"		+11	8/8	7	
				" " " " "		" "	8,769 "	"	" "	"		+28	"	13	
				" " " " "		" "	25,060 "	"	" "	"		5	6/8	18	
				" " " " "		MST	24.7 days	"	" "	"		17	0/8	48	
			AKA-TOL	" " " " "	581	Tumor vol	319 mm^3	"	" "	"		+24	7/7	7	
				" " " " "		" "	563 "	"	" "	"		34	"	13	
				" " " " "		" "	3,517 "	"	" "	"		13	"	24	
				" " " " "		MST	82.6 days	"	" "	"		1	0/7	108	
			RShM-5	" " " " "	582	Tumor vol	144 mm^3	"	" "	"		14	8/8	7	
				" " " " "		" "	1,116 "	"	" "	"		0	"	13	
				" " " " "		MST	40.2 days	"	" "	"		4	0/8	59	
			S37	" 10^6 cells	583	Tumor vol	321 mm^3	"	" "	"		27	7/7	7	
				" " "		" "	1,701 "	"	" "	"		+7	"	13	
				" " "		" "	3,230 "	"	" "	"		+18	"	19	
				" " "		" "	11,199 "	"	" "	"		33	"	30	
				" " "		MST	52.4 days	"	" "	"		25	0/7	90	
			S180	" 50 mg tumor susp	584	Tumor vol	1,094 mm^3	"	" "	"		+25	6/6	7	
				" " " " "		" "	5,125 "	"	" "	"		+57	"	14	
				" " " " "		" "	9,017 "	"	" "	"		+92	5/6	21	
				" " " " "		MST	34 days	"	" "	"		5	0/6	56	
			S37			NA content									100–75
			L5178Y			" "									75
			Ehrlich			" "									250–100
			NK/Ly			" "									100–75

			CaOv					[^{3}H]dThd incl									~ 1,000
			CaOv					NA content									> 1,000
			CaOv					Pro "									< 1,000
12677	Dichloro-allyl lawsone	Boiled starch	LL	"	"	"	"	"	779–781	Tumor vol	2,585 mm^3	sc	3–17	100		12	7/7	7	
				"	"	"	"	"		" "	6,918 "	"	"	"		18	"	16	
			RShM-5	"	"	"	"	"	782	" "	1,003 "	"	3–14	50		+ 53	6/6	7	
				"	"	"	"	"		" "	7,738 "	"	"	"		+ 46	5/6	26	
			AKA-TOL	"	"	"	"	"	783	" "	539 "	"	3–13	"		30	7/7	10	
				"	"	"	"	"		" "	1,411 "	"	"	"		54	"	17	
132319	Indicine-*N*-oxide	Saline	AKA-TOL	"	"	"	"	"	591	" "	1,776 "	ip	2–6	500		39	9/9	7	
				"	"	"	"	"		" "	4,184 "	"	"	"		9	"	13	
				"	"	"	"	"		" wt	13.8 g	"	"	"		0	5/9	42	
			P388	ip, 10^6 cells					592	MST	9.6 days	"	1–9	"		18	0/7	20	
			LL	sc, 50 mg tumor susp					593, 594	Tumor vol	2,585 mm^3	"	3–16	200–500	500	51	7/7	7	
				"	"	"	"	"		" "	6,918 "	"	"	"	"	37	"	15	
				"	"	"	"	"		" "	14 068 "	"	"	"	"	43	"	19	
				"	"	"	"	"		" "	18,893 "	"	"	"	"	40	"	23	
			RShM-5	"	"	"	"	"	595	" "	1,003 "	"	3–17	500		14	"	10	
				"	"	"	"	"		" "	7,738 "	"	"	"		47	5/7	24	
			AKA-TOL	"	"	"	"	"	596	" "	539 "	"	3–12	400		20	7/7	10	
				"	"	"	"	"		" "	1,411 "	"	"	"		68	"	17	
			S37							NA content								500
			L5178Y							" "								"
			Ehrlich							" "								"
			NK/Ly							" "								"
154890	Coralyne sulfoacetate	Saline	P388	ip, 10^6 cells					602	MST	9.6 days	"	1, 4, 7	200		53	0/6	20	
			LL	sc, 50 mg tumor susp					603, 604	Tumor vol	2,585 mm^3	"	3, 6, 9, 12	200–500	200	70	7/7	7	
				"	"	"	"	"		" "	6,918 "	"	" " " "	"		40	"	15	
		Boiled starch	AKA-TOL	"	"	"	"	"	605	" "	1,776 "	"	2–6	75–100	100	70	9/9	7	
				"	"	"	"	"		" "	4,184 "	"	"	"	"	21	"	13	
				"	"	"	"	"		" "	4,002 "	"	"	"	"	36	"	23	
				"	"	"	"	"		" wt	13.8 g	"	"	"	"	30	5/9	42	
			AKA-TOL	"	"	"	"	"	606	" vol	539 mm^3	"	3, 6	200	"	75	7/8	10	
				"	"	"	"	"		" "	1,411 "	"	" "	"		89	6/8	17	
			RShM-5	"	"	"	"	"	607	" "	3,552 "	"	3, 6, 9	120		53	5/7	10	
71851	α-Deoxy-thioguanosine	Boiled starch	L1210	ip, 10^6 cells					645	MST	7.8 days	"	2–6	20–80	80	54	0/3	60	
			La	"	"	"			795	"	8.8 "	"	1–5	80–120	100	2	0/16	"	
			Ca-755	sc, 50 mg tumor susp					647	Tumor vol	1,482 mm^3	"	2–6	60–100	"	97	8/8	7	
				"	"	"	"	"		" "	6,080 "	"	"	"	"	99	"	13	
				"	"	"	"	"		" "	25,001 "	"	"	"	"	79	"	22	
				"	"	"	"	"		MST	24 days	"	"	"	"	82	0/8	65	
			AKA-TOL	"	"	"	"	"	649	Tumor vol	912 mm^3	"	"	80–120	"	+ 22	6/6	7	
				"	"	"	"	"		" "	5,087 "	"	"	"	"	64	"	13	
				"	"	"	"	"		" "	15,054 "	"	"	"	"	61	"	23	
				"	"	"	"	"		" "	21,384 "	"	"	"	"	49	"	29	
				"	"	"	"	"		MST	37 days	"	"	"	"	14	0/6	50	

APPENDIX IV.—*Results of experimental studies in the Soviet Union with drugs developed in the United States [a] (Continued)*

NSC No.	Compound	Drug vehicle	Tumor	Site and inoculum	Expt. No.	Parameter of effect [b]	Controls	Treatment Route	Treatment Schedule, days	Doses, mg/kg/injection Tested	Doses, mg/kg/injection Optimal	Percent ILS or tumor inhibition	Survivors/total	Day of evaluation	ED50, ug/ml
71851	α-Deoxythioguanosine	Boiled starch	RShM-5	sc, 50 mg tumor susp	654	Tumor vol	777 mm³	ip	2–6	60–100	100	2	6/6	8	
				" " " " "		" "	2,729 "	"	"	"	"	21	"	14	
				" " " " "		" "	8,721 "	"	"	"	"	48	5/6	20	
				" " " " "		MST	42 days	"	"	"	"	14	0/6	60	
126849	3-Deazauridine	Boiled starch	L1210	ip, 10^6 cells	585	"	7.8 "	"	"	100–500	500	41	0/3	"	
			La	" " "	792	"	" "	"	2–5	100–300	300	0	0/6	"	
			Ca-755	sc, 50 mg tumor susp	586	Tumor vol	1,482 mm³	"	2–6	200–400	400	87	7/7	7	
				" " " " "		" "	6,080 "	"	"	"	"	52	6/7	13	
				" " " " "		" "	25,601 "	"	"	"	"	4	5/7	22	
				" " " " "		MST	24 days	"	"	"	"	21	0/7	65	
			RShM-5	" " " " "	587	Tumor vol	412 mm³	"	"	200–300	200	82	7/7	7	
				" " " " "		" "	3,228 "	"	"	"	"	87	4/7	14	
				" " " " "		MST	25.7 days	"	"	"	"	7	"	67	
137679	6-Selenoguanosine	Saline	L1210	ip, 10^6 cells	588	"	7.8 "	"	"	20–50	30	63	0/3	60	
			La	" " "	793	"	8.8 "	"	1–5	"	"	17	0/6	"	
			Ca-755	sc, 50 mg tumor susp	589	Tumor vol	1,482 mm³	"	2–6	25–50	25	96	8/8	7	
				" " " " "		" "	6,080 "	"	"	"	"	"	"	13	
				" " " " "		" "	25,001 "	"	"	"	"	46	"	22	
				" " " " "		MST	24 days	"	"	"	"	48	1/8	65	
			RShM-5	" " " " "	590	Tumor vol	412 mm³	"	"	25–35	"	55	7/7	7	
				" " " " "		" "	3,228 "	"	"	"	"	66	6/7	14	
				" " " " "		" "	9,175 "	"	"	"	"	48	"	21	
				" " " " "		MST	25.7 days	"	"	"	"	53	1/7	67	
			AKA-TOL	" " " " "	794	Tumor vol	1,037 mm³	"	"	20–30	20	66	7/7	7	
				" " " " "		" "	3,918 "	"	"	"	"	"	"	13	
				" " " " "		" "	9,086 "	"	"	"	"	69	"	21	
				" " " " "		" "	3,756 "	"	"	"	"	46	"	28	
				" " " " "		MST	50 days	"	"	"	"	40	1/7	108	
154020	Townsend's nucleoside	Boiled starch	L1210	ip, 10^6 cells	608	"	7.8 "	"	"	15–20	15	63	0/3	60	
			La	" " "	802	"	8.8 "	"	1–5	15–30	"	5	0/6	"	
			Ca-755	sc, 50 mg tumor susp	609	Tumor vol	1,450 mm³	"	2–6	10–20	20	45	7/7	7	
				" " " " "		" "	11,233 "	"	"	"	"	+6	"	14	
				" " " " "		MST	21.4 days	"	"	"	"	23	0/7	43	
			AKA-TOL	" " " " "	610	Tumor vol	645 mm³	"	"	15–20	"	93	7/7	7	
				" " " " "		" "	2,537 "	"	"	"	"	66	6/7	13	
				" " " " "		" "	4,561 "	"	"	"	"	40	"	20	
				" " " " "		" "	2,286 "	"	"	"	"	7	5/7	35	
				" " " " "		MST	42 days	"	"	"	"	17	1/7	96	
			RShM-5	" " " " "	611	Tumor vol	777 mm³	"	"	20–30	"	80	6/6	8	
				" " " " "		" "	2,799 "	"	"	"	"	42	5/6	14	
				" " " " "		" "	8,721 "	"	"	"	"	43	"	20	

				" " " " "			" "	16,903	"	"	"	"	"	"	"	27
				" " " " "			MST	42 days	"	"	"	"	5	1/6	60
169780	ICRF-187	Boiled starch	L1210	ip, 10^6 cells		597	"	7.3	"	"	"	50–400	400	96	0/3	22
			La	" " "		807	"	9.4	"	"	1–5	300–500	500	23	0/7	19
			Ca-755	sc, 50 mg tumor susp		598	Tumor vol	1,450 mm^3	"	2–6	"	"	94	7/7	7
				" " " " "			" "	11,233	"	"	"	"	96	6/7	14
				" " " " "			" "	14,347	"	"	"	"	77	"	18
				" " " " "			MST	21.4 days	"	"	"	"	53	0/7	43
			AKA-TOL	" " " " "		599	Tumor vol	645 mm^3	"	2–8	300–350	300	50	7/7	7
				" " " " "			" "	2,537	"	"	"	"	83	"	13
				" " " " "			" "	4,561	"	"	"	"	73	"	20
				" " " " "			" "	12,286	"	"	"	"	62	5/7	35
				" " " " "			MST	42 days	"	"	"	"	4	0/7	100
			RShM-5	" " " " "		600	Tumor vol	777 mm^3	"	2–6	300–400	"	49	5/6	8
				" " " " "			" "	2,799	"	"	"	"	41	6/6	14
				" " " " "			" "	8,721	"	"	"	"	61	"	20
				" " " " "			" "	6,903	"	"	"	"	52	5/6	27
				" " " " "			MST	42 days	"	"	"	"	8	1/6	60
			PRZh	im, " " " "		601	Tumor vol	5,964 mm^3	"	"	"	"	35	6/6	7
				" " " " "			" "	15,093	"	"	"	"	31	"	13
				" " " " "			" "	29,111	"	"	"	"	2	"	23
				" " " " "			MST	36 days	"	"	"	"	31	0/6	108
172112	Spirohydantoin mustard	Boiled starch	L1210	ip, 10^6 cells		356	"	7.3	"	"	"	10–25	15	78	0/3	22
			La	" " "		808	"	8	"	"	1–5	5–15	10	79	1/7	17
			Ca-755	sc, 50 mg tumor susp		357	Tumor vol	522 mm^3	"	"	5–20	5	65	7/7	7
				" " " " "			" "	12,666	"	"	"	"	"	"	14
				" " " " "			" "	33,666	"	"	"	"	6	6/7	23
				" " " " "			MST	22.7 days	"	"	"	"	34	0/7	60
			RShM-5	" " " " "		800	Tumor vol	244 mm^3	"	2–6	4–8	8	56	6/6	7
				" " " " "			" "	2,196	"	"	"	"	18	"	13
				" " " " "			" "	6,059	"	"	"	"	16	5/6	21
				" " " " "			MST	34.2 days	"	"	"	"	22	0/6	60
176319	Quinolinium derivative	Boiled starch	L1210	ip, 10^6 cells		645	"	7.8	"	"	"	10–40	10	483	1/3	"
			La	" " "		809	"	8.8	"	"	1–5	5–15	"	150	1/6	"
			Ca-755	sc, 50 mg tumor susp		647	Tumor vol	1,482 mm^3	"	2–6	"	"	71	8/8	7
				" " " " "			" "	6,080	"	"	"	"	34	7/8	13
				" " " " "			" "	25,001	"	"	"	"	+21	"	22
				" " " " "			MST	24 days	"	"	"	"	2	0/8	65
			AKA-TOL	" " " " "		649	Tumor vol	912 mm^3	"	"	5–8	8	62	6/6	7
				" " " " "			" "	5,087	"	"	"	"	59	"	13
				" " " " "			" "	15,054	"	"	"	"	66	5/6	23
				" " " " "			" "	21,384	"	"	"	"	59	"	29
				" " " " "			MST	37.0 days	"	"	"	"	4	0/6	50
			RShM-5	" " " " "		654	Tumor vol	777 mm^3	"	"	5–7	5	+27	7/7	8
				" " " " "			" "	2,799	"	"	"	"	+39	"	14
				" " " " "			" "	8,721	"	"	"	"	+6	"	20
				" " " " "			MST	42 days	"	"	"	"	10	0/7	60

APPENDIX IV.—*Results of experimental studies in the Soviet Union with drugs developed in the United States* [a] *(Continued)*

NSC No.	Compound	Drug vehicle	Tumor	Site and inoculum	Expt. No.	Parameter of effect [b]	Controls	Treatment: Route	Treatment: Schedule, days	Doses, mg/kg/injection: Tested	Doses, mg/kg/injection: Optimal	Percent ILS or tumor inhibition	Survivors/total	Day of evaluation	ED50, ug/ml
176319	Quinolinium derivative	Boiled starch	PRZh	im, 50 mg tumor susp	655	Tumor vol	5,964 mm³	ip	2–6	5–7	5	38	7/7	7	
				" " " " "		" "	15,093 "	"	"	"	"	20	"	13	
				" " " " "		" "	29,111 "	"	"	"	"	0	6/7	23	
				" " " " "		MST	36 days	"	"	"	"	9	1/7	100	
178248	Chlorozotocin	Boiled starch	L1210 La	ip, 10^6 cells	351	"	7.3 "	"	"	2.5–10	7.5	156	1/3	22	
				" " "	810	"	8 "	"	1–5	5–10	"	10	0/6	17	
			Ca-755	sc, 50 mg tumor susp	352	Tumor vol	522 mm³	"	"	3–9		+ 15	7/7	7	
				" " " " "		" "	12,666 "	"	"	"		30	"	14	
				" " " " "		" "	33,779 "	"	"	"		34	"	23	
				" " " " "		MST	22.7 days	"	"	"		29	0/7	60	
			RShM-5	" " " " "	353	Tumor vol	412 mm³	"	2–6	3–5	3	39	7/7	7	
				" " " " "		" "	3,228 "	"	"	"	"	73	"	14	
				" " " " "		" "	9,175 "	"	"	"	"	72	"	21	
				" " " " "		MST	25.7 days	"	"	"	"	91	0/7	67	
			AKA-TOL	" " " " "	797	Tumor vol	1,037 mm³	"	"	"	5	64	7/7	7	
				" " " " "		" "	3,918 "	"	"	"	"	85	"	13	
				" " " " "		" "	9,086 "	"	"	"	"	83	6/7	21	
				" " " " "		" "	3,756 "	"	"	"	"	62	5/7	28	
				" " " " "		MST	50 days	"	"	"	"	10	0/7	108	
249992	Cain's acridine derivative	Boiled starch	L1210	ip, 10^6 cells	358	"	7.3 "	"	"	5–20	10	51	0/3	22	
			Ca-755	sc, 50 mg tumor susp	359	Tumor vol	1,450 mm³	"	"	5–15	5	80	7/7	7	
				" " " " "		" "	11,233 "	"	"	"	"	12	6/7	14	
				" " " " "		" "	14,347 "	"	"	"	"	+ 36	"	18	
				" " " " "		MST	21.4 days	"	"	"	"	24	0/7	43	
			AKA-TOL	" " " " "	801	Tumor vol	1,037 mm³	"	"	4–6	6	71	7/7	7	
				" " " " "		" "	3,918 "	"	"	"	"	58	"	13	
				" " " " "		" "	9,086 "	"	"	"	"	54	"	21	
				" " " " "		" "	3,756 "	"	"	"	"	27	"	28	
				" " " " "		MST	50 days	"	"	"	"	18	0/7	108	
			RShM-5	" " " " "	286	Tumor vol	412 mm³	"	"	5		0	7/7	7	
				" " " " "		" "	3 228 "	"	"	"		52	6/7	14	
				" " " " "		" "	9,175 "	"	"	"		46	"	21	
				" " " " "		MST	25.7 days	"	"	"		53	0/7	67	
			La	ip, 10^6 cells	811	"	8 "	"	1–5	5–15	5	10	0/6	17	
95466	1-(2-Chloroethyl)-3-(2,6-dioxo-3-piperidyl)-1-nitrosourea	Boiled starch	L1210 La	" " "	354	"	7.3 "	"	2–6	1–2	2	109	0/3	22	
				" " "		"	8 "	"	1–5	2–5	5	16	0/7	17	
			Ca-755	sc, 50 mg tumor susp	355	Tumor vol	522 mm³	"	2–6	1.5–4	4	80	7/7	7	
				" " " " "		" "	12,666 "	"	"	"	"	66	"	14	
				" " " " "		" "	33,779 "	"	"	"	"	75	5/7	23	
				" " " " "		MST	22.7 days	"	"	"	"	72	1/7	90	
			AKA-TOL	" " " " "	798	Tumor vol	1,037 mm³	"	"	1.5–3	3	80	7/7	7	
				" " " " "		" "	3,918 "	"	"	"	"	81	"	13	

				" " " " "			" "	9,086	"	"	"	"	"	56	"	21
				" " " " "			" "	3,756	"	"	"	"	"	50	"	28
				" " " " "			MST	50	days	"	"	"	"	40	0/7	108
			RShM-5	" " " " "		799	Tumor vol	244	mm^3	"	"	1–1.5	1.5	33	5/5	7
				" " " " "			" "	2,196	"	"	"	"	"	63	"	13
				" " " " "			" "	6,059	"	"	"	"	"	37	"	21
				" " " " "			MST	34.2	days	"	"	"	"	6	0/5	60
45388	Dacarba-zine	Boiled starch	L1210	ip, 10^6 cells		550, 551	"	7.3	"	"	2, 6	125–225		15	0/6	13
				" " "			"	8.9	"	"	1–6	50		28	0/7	12
			La	" " "		812	"	8	"	"	1, 5	150–200	200	19	0/6	17
			MOPC 406	" " "		552	"	14.9	"	"	4–10	80		0	0/8	14
			LL	sc, 50 mg tumor susp		553	Tumor vol	2,693	mm^3	"	2–6	50		13	7/7	7
				" " " " "			" "	14,775	"	"	"	"		27	"	13
				" " " " "			" "	18,001	"	"	"	"		15	1/7	20
				" " " " "			MST	21.3	days	"	"	"		6	0/7	35
				" " " " "			Tumor vol	2,693	mm^3	"	2, 6	200		44	7/7	7
				" " " " "			" "	14,775	"	"	" "	"		59	5/7	13
		Saline		" " " " "			" "	18,001	"	"	" "	"		6	1/7	20
				" " " " "			MST	21.3	days	"	" "	"		23	0/7	35
			Ca-755	" " " " "		554, 555	Tumor vol	443	mm^3	"	2–4	100		44	6/6	7
				" " " " "			" "	5,549	"	"	"	"		+ 20	"	13
				" " " " "			MST	22.3	days	"	"	"		0	0/6	39
				" " " " "			Tumor vol	443	mm^3	"	2	175		54	6/6	7
				" " " " "			" "	5,549	"	"	"	"		4	"	13
				" " " " "			MST	22.3	days	"	"	"		0	0/6	39
			AKA-TOL	" " " " "		556–558	Tumor vol	466	mm^3	"	2, 6	150–225	175	18	8/8	7
				" " " " "			" "	1,930	"	"	" "	"		83	"	13
				" " " " "			" "	4,139	"	"	" "	"		61	"	20
				" " " " "			" "	8,787	"	"	" "	"		39	"	27
				" " " " "			MST	52	days	"	" "	"		8	0/8	104
			RShM-5	" " " " "		559, 560	Tumor vol	95	mm^3	"	2–6	100		37	6/6	7
				" " " " "			" "	2,157	"	"	"	"		+ 16	"	13
				" " " " "			" "	4,662	"	"	"	"		27	5/6	20
				" " " " "			MST	54.8	days	"	"	"		30	0/6	79
				" " " " "		561, 562	Tumor vol	95	mm^3	"	2, 6	175–200	"	34	7/7	7
				" " " " "			" "	2,157	"	"	" "	"	"	56	"	13
				" " " " "			" "	4,662	"	"	" "	"	"	51	6/7	20
				" " " " "			MST	54.8	days	"	" "	"	"	22	0/7	79
			PRZh	im, " " " "		563	Tumor vol	2,937	mm^3	"	2–6	75		40	8/8	7
				" " " " "			" "	7,230	"	"	"	"		43	"	13
				" " " " "			" "	9,082	"	"	"	"		+ 19	"	20
				" " " " "			" wt	8.8	g	"	"	"		+ 46	"	28
			S37	sc, 10^6 cells		564, 566	" vol	519	mm^3	"	2, 6	175		19	6/6	7
				" " "			" "	2,773	"	"	" "	"		37	"	13
				" " "			" "	5,033	"	"	" "	"		+ 58	"	20
				" " "			MST	53.8	days	"	" "	"		9	3/6	52

[a] ED50 = median inhibitory concentration; MST = mean survival time; LL = Lewis Lung; susp = suspension; [^{3}H]dTHd incl = tritiated thymidine included; NA = nucleic acid; Pro = protein.

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